Modern Management

in

CLINICAL MEDICINE

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By

F. KENNETH ALBRECHT, M.D.

S. A. Surgeon, U. S. Public Health Service, Kansas
State T[illegible] [illegible] Center and Formerly Clinical
Director, U. S. Marine Hospital
Baltimore, Md.



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FOREWORD

In projecting a new medical book, it is essential that the author assure himself that there is a need for such a book, that it will bring to the medical practitioner something which he is unable to find in textbooks on similar subjects; that it will present new facts and the newer developments of medical science; or that it will present already known facts in a form that will make them readily available so that the reader may consume a minimum of time in obtaining the necessary information on a particular subject.

The author conceived this volume with these essentials in mind. He had been impressed with the fact that there was a need for a medical book that would present to the profession the new advancements and techniques in the practice of medicine in a form in which the subject matter would be condensed, simplified and at the same time presented in an adequately comprehensive manner. It has been the sincere effort of the author to produce a volume in which the established medical facts that have been proven valuable by the experiences of time would be combined with the recent discoveries in diagnostic procedures, special techniques and therapy and presented in a readily available form.

Dr. Albrecht stresses the fact that he is a reporter and that this volume is a compilation of medical facts, obtained from many sources only after a thorough and painstaking search and an adequate sifting of an extensive literature. His own knowledge, experiences and observations in the field of internal medicine have been added to these compiled facts to give a note of freshness and originality to the work. He has exercised judgment in his selection of material, including in its contents the most recent developments in tropical diseases, vitamin deficiencies, geriatrics and chemotherapy.

The form of presentation followed throughout the book is unique and permits the practitioner with limited time for reading to obtain quickly and in a succinct form the recent, pertinent facts relative to diagnosis, differential diagnosis and treatment. The discussion of treatment is elaborate enough to be adequately inclusive and brief enough to guide the physician along the ways of security in the conduct of his cases. The use of the trade names of drugs and pharmaceutical preparations will add much to the peace of mind of the clinician and should add to the ease with which he is able to put into clinical practice his own knowledge of the treatment of diseases.

This book should prove to be of value to students, interns, physicians in general practice and clinicians practicing in the specialties. They will have at hand a ready reference in which presentations, shorn of all non-essentials, may be consulted with little difficulty.

Dr. Albrecht's original reasons for writing this book seem justified in the ultimate achievement. He has produced well and deserves much credit and a word of thanks for his energy, perseverance, unlimited patience and his desire to contribute to his colleagues a work which should simplify the practice of medicine and save the time of much-overworked practitioners of medicine.

ALPHONSE MCMAHON
Commodore, Medical Corps
United States Naval Reserve,
Chief of Medicine
U. S. Naval Hospital
Bethesda, Maryland

PREFACE

This volume is intended for the doctor's office, not his library. Its purpose is to present, in each case, a clear picture of the rationale of therapy together with useful and usable information in detail about the technique of therapy. If, for instance, drugs are mentioned, the information about dosage, toxic effects, contraindications, and everything necessary for the physician to know is also included. The conviction that this is what physicians and students seek in books has been the motivation for this one. Procedures and case-study methods outlined here conform to medical practice as taught in accredited medical schools and utilized in the larger clinics throughout the nation.

Yet it is not the author's intention to suggest a standardized routine handling of patients or a slavish following of the procedures described. Any attempt to streamline the practice of medicine must end in failure; there are no short-cuts in medicine. The foundation stone of every diagnosis remains a careful and thoroughly well-organized case history and an equally painstaking physical examination. The goal is the treatment of the patient as a whole first, and of the disease afterward.

To quote all the sources of material would require much additional space and would serve little purpose. It is hoped that the bibliographies at the end of each chapter will be adequate. Only the latest have been used and the references have actually been consulted by the author. In a few instances, i.e., tropical diseases of post war significance, optional reading matter has been listed for the benefit of those interested, and it is hoped that the readers will consult the original articles and standard texts when possible and when time permits. No book is perfect and no one is more keenly aware of the imperfections of this one than is the author, who will appreciate criticism and suggestions for the betterment of this volume. While he assumes all responsibility for the manner of presentation and the material contained within its pages, its true writers are the many who have contributed to medical literature in the last few years.

In particular, I want to extend my sincere gratitude and appreciation to Surgeon Seward E. Miller, U. S. Public Health Service, Chief of the Department of Pathology, U. S. Marine Hospital, Baltimore, for his helpful suggestions, his constructive criticism and valuable painstaking assistance in both reviewing and writing portions of the manuscript. Without his help at times, and moral support always, the task could scarcely have been performed. I am indebted to the Peter Bent Brigham Hospital of Boston for the permission to reproduce several of their out patient forms, and to the Mayo Clinic for permission to reproduce their case history form on neurology. Dr. John F. Wirth, Director of the tumor clinic of the U. S. Marine Hospital, Baltimore, furnished some clinical photographs. Dr. Harry M. Robinson of the University of Maryland generously furnished most of the photographs used in the chapter on common skin disorders. Dr. Antonio Mayoral of the U. S. Marine Hospital and Tulane University, New Orleans, La., and Dr. J. H. Booth of the U. S. Marine Hospital, Baltimore, both generously contributed x-ray films from their respective departments of radiology. Technician John Cuidry photographed most of the roentgen films used. Surgeon T. M. Burkholder furnished many of the clinical photographs on venereal diseases. The Barton Stamp Co. of New York City furnished the rubber anatomical stamps used in the diagrams throughout the book. Original drawings and charts were done by Mrs. Madge Williamson and William Loeschel.

To the many officers of the United States Public Health Service and the interns of the United States Marine Hospitals whose assistance and constructive criticism have been freely given, I desire to express my sincere appreciation.

Finally, I am indebted to Dr. Norman B. Taylor, consultant editor of the Williams & Wilkins Company and co-author of *The Physiological Basis of Medical Practice*, who reviewed and edited the typescript in full and painstakingly.

F. K. A.

Dec. 15, 1945

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Chapter I

THE CASE HISTORY

General Considerations

Well written, complete and evenly balanced case histories are a prime necessity. Completeness and accuracy are of vital importance, particularly since claims for compensation may be based on the record. Poor histories usually fall into one of two classes: profusely written but with important facts omitted or only sketchily outlined, or descriptively good but entirely too brief, with neglect of much that is positively essential.

Legible writing is imperative. A history peppered with abbreviations that only the person who made it can decipher (and perhaps not even he after a few weeks) may be wholly useless, for hours spent in the attempt to decode the scrawl and symbols may still leave grave doubt about what was intended.

All results of the physical examination should be set down completely and in detail. It is best to begin with the *height, weight* and *general appearance* of the patient. Then proceed in orderly fashion to the *head*, making a report of the condition of the *eyes, ears, nose, throat* and *mouth*; then follow with the *chest, lungs, heart, abdomen, genitalia, anus, upper and lower extremities*, and *bones and joints*. The *skin* and *nervous system* should not be overlooked. The *blood pressure, pulse rate* and *respiratory rate* should always be recorded. The habit should be acquired of writing down these entries and the results afterward, *even if they are negative*. Negative statements are often of great value; they indicate that the particular detail was covered and the symptom or sign was definitely known not to have been present at the time of the examination.

All *injuries* should be carefully described in order to convey an accurate picture of the amount of damage inflicted. The *location* of a wound, contusion or burn should be stated definitely, giving the anatomical site, appearance, degree or depth. In all cases the *amount or degree of loss of function* produced by the injury should be stated. It is a good practice to use sketches or rubber anatomical stamps to describe such lesions.

The diagnosis can be made from a well taken history in from 60 to 70 per cent of cases. Often the only clue to the diagnosis is in the history. Therefore when doubt arises, it is well to review the history. One should also refrain from making a mental diagnosis of the patient's ailment immediately upon meeting him for the first time. Snap diagnoses are usually wrong and the patient resents the physician's pre-conceived ideas about his illness. A combative spirit results and a mental barrier is erected between the doctor and the patient which cannot easily be broken down. The physician must get a clear story, free from bias and leading inquiry, and if the history is to have any diagnostic value, the symptoms must be detailed in chronological order.

The history is not complete if it concerns itself only with symptoms. An attempt should be made to determine the patient's individual threshold to pain, his constitutional and psychic diathesis, and whether the basis of his symptoms is organic or functional. Often the diagnosis of *neurosis* is made from the history alone. The following features will be noted in questioning neurotic patients: (1) The patient may have great difficulty in stating what the chief complaint is, and his recital may be punctuated by frequent irrelevant remarks. (2) He may come prepared with a long list of carefully written complaints and symptoms, in some cases with the date, hour and even minute of occurrence. (3) Great emotional instability may be shown as his troubles are recounted, by wringing of the hands or by weeping. (4) Such patients may bring in a sample of mucus which they have passed per anum and are positive that it is the lining of their bowels. Their chief complaint may be any of the following: a lump in the throat, inability to get the breath, a jumping or fluttery feeling in the abdomen, abdominal distress and headaches that can only be relieved by constant catharsis, and lastly, vague abdominal pains that have survived several operations.

Some physicians prefer to examine their patients before composing and writing the

history This enables them more accurately to evaluate the symptoms, the significance of which may have been obscure prior to the examination It also permits the physician to place each symptom in the patient s history in a position commensurate with its diagnostic importance It follows that should a patient come to the office for the treatment of a cold or to have a wart removed, a complete detailed case history is quite unnecessary, when a patient presents himself with a condition which requires careful study and the waiting room happens to be full of clamoring patients it is wise to ask him to come back later when more time can be spent upon him It is unfortunate that too many of us regard history taking as a waste of time We are apt to fall into the error of treating symptoms rather than the underlying diseases Time spent in making a complete history and physical examination is never wasted or lost, the information gained in this way and *recorded* can be consulted from time to time and forms a valuable base line study for future reference

There are some from whom it is difficult to elicit a satisfactory history When a patient speaks little or no English there is a temptation to spend too little time on the history and to proceed instead with the physical examination This leads to diagnostic inaccuracy and one will do well to procure an interpreter and spend as much time as may be necessary to evaluate the patient's complaints There are others who do not seek medical advice until they have become disabled and far along in their illness They remember little if anything concerning their symptoms, the onset of their illness the progression of the symptoms or the time of appearance of any complications Almost all direct questions are answered in the negative, they only know that they were or are sick or had the 'misery' In such patients one is compelled to rely more on the physical examination and certain laboratory studies in arriving at a diagnosis This is the only type of case where one is justified in letting the laboratory or technical procedures make the diagnosis and direct the treatment In any other type of patient this habit is to be deprecated, for when this is done the patient as a rule loses his identity and simply becomes the case with the ulcer, etc The consequence is that many errors are made and many psychological injuries are inflicted

In mental disease it is often very difficult to secure a satisfactory history It is usually time consuming, and frequently the information that is gleaned from the patient is of little or no value Relatives frequently give no help, many choosing to have the doctor gain what information he can In such circumstances it may help to inquire whether the patient sought the doctor of his own free will or was sent or brought to the doctor by his relatives or friends

Finally in composing histories it is well to remember that the data given by the patient should be used but the physician should analyze and edit it before incorporating it in the clinical history A disorderly jumble of what the patient said is almost worthless Before arriving at a diagnosis it is well for the doctor to read over the history carefully before making even a tentative diagnosis In order that the physician may get a true value and the right perspective of the patient s problem the following points should be established early while taking the history (1) The major complaint (2) Its duration (3) What has made the patient decide to come to the physician (4) Has the condition which involved the major complaint disabled the patient? (5) Are any lawsuits pending?

The Use of the Clinical Laboratory

There has been a tendency lately to emphasize the laboratory side of medicine at the expense of the clinical All physicians have not the facilities of a teaching hospital where tests can be ordered at will and with so little inconvenience to the clinician himself that they too often are undertaken without sufficient thought as to their necessity Moreover many patients do not have the money to pay for such tests others are not concerned enough about their condition to want to pay for them In many instances the physician with a little effort can make the diagnosis with little aid from the laboratory It is at the bedside where opinions should be gained and in the laboratory where they are confirmed None will deny that it is a measure of a doctor s ability if he can consistently make correct diagnoses with the aid of a minimum number

of laboratory tests The author has seen patients, ill fed and undernourished, with scarcely enough money in their pockets to furnish the necessities of life, sent for roentgen studies of the stomach costing fifteen dollars simply because they had a 'pain in the stomach'

Alvarez believes physicians should be making more than half of their diagnoses without the aid of roentgenologic or laboratory reports He points out the value of taking a little time and of shrewd questioning and, equally important, after having made the diagnosis on the basis of history and examination of putting more trust in the diagnosis instead of ordering a number of tests merely to confirm the conclusions Many physicians place too much emphasis on the results of laboratory tests One should never change a clinical diagnosis merely because it is not supported by laboratory findings Similarly diagnoses based upon laboratory evidence alone rest upon an insecure foundation

Major (1) has stressed the current tendency to neglect the simpler methods of diagnosis for new ones Some excerpts from his paper bear repeating

> Inability to walk in the dark and lightning pains in the legs are as important in the diagnosis of tabes dorsalis as is a positive Wassermann
>
> Confronted with a history of increasing sluggishness inability to keep warm at night increasing dryness of the hair and skin one can diagnose myxedema without doing a basal metabolic test
>
> In many diseases the location and character of pain is an important clue in diagnosis In angina pectoris the physical examination may show nothing There is no registering device for pain
>
> Percussion will demonstrate cardiac enlargement better than a study of axis deviation and the electrocardiogram Percussion will demonstrate lateral deviation of the heart as accurately as the roentgen study
>
> Auscultation of the heart gives better evidence of mitral stenosis aortic insufficiency and of the less common lesions than does any instrument of precision
>
> The glucose tolerance test is not essential to the diagnosis of diabetes mellitus Usually the diagnosis may be clinched by the history and the demonstration of *sugar in the urine* It is more important to know whether a patient is secreting sugar during a twenty four hour period and if so how much than it is to know the exact height of his blood sugar at the precise moment that the blood is drawn
>
> Chemical methods have increased our knowledge of kidney disease but are not able to diagnose a failing kidney until three fourth of the *glomeruli* have been destroyed In the diagnosis of diseases of the kidney the sheet anchors are still the sphygmomanometer and the examination of the urine for albumin and casts
>
> Pain and chronicity are characteristic of duodenal ulcer Food or alkalies will remove the pain which comes on two to four hours after meals One need not refuse to treat a patient with ulcer because x ray studies and gastric analyses cannot be made

The Medico-Legal Importance of the Case History and Physical Examination

It is recognized that a complete all inclusive history is of great medico-legal importance since many patients base their claims solely upon the hospital record Compensation awards insurance claims, and disputes frequently arise and one may be asked the question "Is the patient s present disability the result of the described or alleged injury?" Because one is compelled to answer the question with a reasonable degree of certainty" the thoroughness with which we record and study the findings of our cases immediately becomes apparent

In the case of accidents one must *know* and *record* the exact *hour place* and *date* that it occurred It is well to record in the *patient s own words* how the accident happened as well as to state also in his own words the chief complaint at the time of his first visit A detailed description of previous trauma and accidents with dates of hospitalization if any, is helpful since from such information the degree of disability referable to the present injury can be estimated more accurately

In all industrial accidents complete general physical examinations should be made and recorded The record should include the results of routine examinations of the blood and urine It is embarrassing to have to admit in court that pupillary reactions tests for vision blood pressure determinations and a neurological examination have not been done One must answer the question Is there any evidence of pre existing injury or disease? and that is impossible without a thorough general physical examination Measure all swellings with a tape measure and record the measurements on the patient s chart If ecchymosis is present by all means record the fact describing its location and extent All *deformities* should be described fully and where *disabilities or loss of function* are found, they should be recorded in percentages or degrees *Point*

tenderness is important as a diagnostic sign in articular lesions Describe all scars, both new and old, accurately Note and record their condition as to adherence, depth, color and tenderness Opinions as to causal relationship may depend upon the records of those rendering the first emergency treatment, thus again the importance of keeping a careful accurate record of the examination and the history is at once apparent

There remains a large group of cases in which determination of the cause of the diseased state will depend almost entirely upon the findings at operation It is good practice to dictate a description of the operation immediately following the operative procedures It is desirable to include negative findings The presence or absence of newly formed or old adhesions edema or hemorrhage is of value and should be recorded

It is generally admitted that a severe injury will aggravate a preexisting hypertrophic osteoarthritis It is hard to conceive of any pathological lesion which might not, under certain circumstances be aggravated indirectly or directly by an injury In joints such as the knee, such aggravations are accompanied by effusions which if the part is rested for a few weeks usually subside It is assumed that similar changes occur in hidden joints, such as the spine and pelvis An aggravation in back injuries should cease within two months

Trauma should be questioned as a causative factor in the following conditions

- Appendicitis
- Cholangitis
- Cholecystitis
- Cysts in areas where congenital lesions are likely to be found
- Duodenal ulcer
- Gastric ulcer
- Hemorrhoids
- Renal calculus
- Renal displacements
- Pilonidal cyst

Other Items of Importance in the Case History

PROGRESS NOTES ON THE CASE RECORD

The progress of the disorder should be detailed If the patient is acutely ill all important symptoms should be chronologically recorded, and usually a note on the chart will be necessary every day or possibly even oftener Charts may be narrative in style and should show clearly the events and findings upon which the diagnosis and treatment or changes in the latter are based It is well to note the patient's condition every time a new treatment is begun or a medication discontinued, or when any other therapeutic measures have been instituted To avoid the monotonous repetition of 'no complaints" or 'condition the same, one may describe various individual symptoms or conditions such as the patient's mental state, his gain or loss of weight, his appetite, or his ability to sleep

DISCIPLINARY INFRACTIONS IN SERVICE HOSPITALS

In the military services all disciplinary infractions should be recorded in the history as promptly as possible This is important in those patients who have been continually guilty of minor offenses for the cumulative evidence sometimes necessitates their discharge though no single act would justify or warrant such action The records should also explain any unusual event that has occurred This is very important in order to safeguard the reputation of the institution or of the physician

LOSS OF RECORD

Sometimes the whole or part of the history may be lost or disappear The file should be re written as well as possible from memory and the circumstances concerning the loss fully described

DISCHARGE NOTES

One of the most common defects is the failure to describe in detail the condition of the patient upon his discharge The discharge note should give a clear picture of the patient s actual condition not only in cases of injury but in *all* cases

Symptom Review in the Medical History

To aid in the writing of good histories a list of major symptoms are listed with important points to be covered in discussing each symptom The following are covered in alphabetical order

CHILLS

Onset Sudden or gradual? What doing at the time? Previous similar episode?

Frequency Every 24—48—or 72 hours? Mild or severe? Nocturnal?

Duration For past days, weeks or months? How long lasting?

Followed by Fever? Profuse sweating? Jaundice?

Associated Symptoms Nausea vomiting tenderness, steady or colicky pains in the groins or over the kidneys or gall bladder? Diarrhea? Continued fever? Cough? Progression? History of malaria? What treatment already given and with what success?

COLDS—SORE THROATS

Frequency? Duration of attacks? Does cold start with a sore throat or in the nose? Are attacks accompanied by sneezing itching, or watering of the eys? Is there a history of hay fever asthma, hives or eczema? Do you have trouble in getting rid of a cold? Is there a productive sputum? Is it foul smelling? Is there any loss of weight lately? When was last roentgen study of the chest?

COLIC

Mild or severe? Onset sudden or gradual? Previous attacks? Site of pain? Radiates to? *Is the pain constant or intermittent?* Is it relieved by pressure? Does it make the patient restless or quiet? Is any constipation or diarrhea present? Is jaundice present now? Is there a recent or past history of jaundice? Any previous gall bladder or kidney trouble? History of stones passed? Is there pain in the groin or in area of the genitalia? Is there pain on micturition? Can the patient eat raw apples melon, fats or gravies or raw vegetables without discomfort?

CONSTIPATION

Duration? Do attacks of constipation alternate with diarrhea? Is blood or mucus passed in the stools? Is the patient an habitual user of cathartics and if so what are they and how often are they used? How many meals are eaten daily? Fast or slow eater? Does patient get enough sleep at night? Excessive smoking habits? How much water or fluids are drunk daily?

CONVULSIONS

Are they confined to one side or are they unilateral? If bilateral, are the two sides affected equally or unequally? Are muscles rigid or thrown into violent jerky motion? How often do the attacks occur? How long do they last? Is the patient conscious during the attack? Involuntary feces or urine passed? Was onset accompanied by a cry or preceded by an aura? Is there a history of epilepsy? Any foaming at the mouth? Any previous attacks? Vomiting? Headaches? Blindness? Blurred vision lately or now? Twitching of muscles of hands or of face? Abuse of alcohol? Any recent mental changes? Tremor of hands or tongue? Rapid loss of unconsciousness with complete relaxation? Unequal or contracted pupils? Onset in jaws or neck? Recent wound or cut? History of recent infected wound? Is the abdomen rigid?

DIARRHEA

Onset Gradual or sudden? Frequency? Morning or evening? Bloody—watery—painful—soft—well formed—small or large amounts? Offensive or foul odor? Preceded followed or accompanied by cramps? Do bowel movements give relief?

Contents and Description Undigested food—worms—much gas—bright red blood—dark red blood—black tarry blood—clay color—clots?

Associated Symptoms Collapse? Cramps? Jaundice? General abdominal pain? Nausea? Vomiting? Cold Sweats? Chills? Constipation? Delirium? Voluntary or involuntary bowel movements? Alternating with constipation? Colicky pain? Abdominal distension? Thirst? History of drinking much fluids (cold) lately?

Appearance of Tongue Coated—furred—dry—moist—fissured? What treatment has been given to date and with what results?

FEVER

Degree? Course? Continuous? Remittent? Intermittent? Undulating of Pel

Ebstein type? Anything unusual in the occupational or dietary history for the period covering several days prior to the patient's first visit Was the onset sudden or gradual? Recent medications?

Associated Symptoms Rigors (mild or severe), nausea vomiting pain (describe location and course), cough, jaundice, hot, dry skin or moist cold skin? Diarrhea? Colicky pain? Skin rash? History of loss of consciousness—paralysis—pin point pupils? Painful glands, sore throat, muscle or joint pain?

Other Progressive or static course? Recent vaccination or food indiscretion? What treatment already given and with what results?

HEADACHE

Is it due to structural disease (*organic*), or to a psychologic maladjustment (*functional*)? If it is of organic origin is it of intracranial or extracranial origin? For example, is it due to a brain tumor, a ruptured cerebral aneurysm fibrositis, or sinus disease If it is of intracranial origin it is due to cerebral or extracerebral disease, thus is it due to brain abscess hydrocephalus tumor, etc , or, leptomeningitis, acute or chronic as from tuberculosis or syphilis? Is it due to diseases of the dura, pachymeningitis hemorrhagica late subdural hematoma or subarachnoid hemorrhage?

Location Is it over the eyes back of the head or ears?

Onset Sudden or gradual? How long troubled? Static or progressive?

Frequency One or more a day week or month? Time of day or night? Does the pain awaken patient from sleep? Is it brought on or aggravated by sudden change in position jolting or straining? Is it the sole symptom?

Associated Symptoms Diplopia—hemiparesis—facial paresis—ataxia—loss of visual acuity—vomiting—reflex changes and mental disturbances? Any advance notice of nausea or vomiting? Glasses worn lately? Any recent sinus trouble? Does reading playing cards or seeing movies cause or aggravate an already existing headache? Is it made worse by stooping over? Is it relieved by aspirin gynergen or other drugs? Unilateral or bilateral eye pain? Suboccipital tenderness or rigidity of the neck? Drowsy? Depression? Inattention? Difficulty in concentration? Forgetfulness? Insomnia? Is the headache increased by making decisions and doing work? Is it worse in crowds theatres or trains? Is it relieved by some new regime of therapy or by reassurance? Is there any connection with menstrual or gastrointestinal function?

Other Any recent injury? Describe fully with dates and period of hospitalization as well as treatment received and with what success Is the patient able to work? Are there any law suits pending? Is there a history of marital difficulty? Is there any relation to exposure to drafts sitting in an air-cooled movie washing or drying the hair driving the car for long distances, sewing, typing, or other occupation strain? Are the headaches paroxysmal?

HEMORRHAGE

Location? Bright red or dark color of blood? Slight or profuse? Onset sudden or gradual? Previous similar episodes? Spotting? (Consider all vaginal bleeding after the menopause as cancer until proved otherwise) Is the bleeding free spurting oozing controlled by pressure or tourniquet or by elevation of the part? Is the patient conscious rational drowsy or stuporous? Is there any temperature elevation? Chills?

Associated Symptoms and Signs Blindness weakness fainting pallor, air hunger jaundice tachycardia purple or hemorrhagic areas under the skin? Has bleeding followed retching? By how long a time? Tarry stools? Did fainting follow the passage of tarry stools? Did patient return to work soon? Were any iron or bismuth powders being taken at the time? Was abdominal discomfort present unchanged or relieved after passing black tarry stool? Did the patient note any relief while on a Sippy regime?

HOARSENESS

Duration? Was onset sudden or gradual? Aphonia at any time? For how long? Was attack of hoarseness preceded by a head cold or a sore throat? History of discomfort in larynx? Productive cough? Dysphagia? Pain related to the use of the voice? Pain on breathing?

JAUNDICE

Onset sudden or gradual? Location? Any previous similar episodes? Color canary yellow—deep yellow—almost black? How long present? Any colicky pain? Locate and describe Duration of pain? Recur how often? Any recurring chills or fever? Sweating? Color of stools? Does urine stain clothes? Any nausea—vomiting—headache—furred tongue—itching? What medications have been taken lately? Any recent arsenicals lately or other treatment for syphilis?

PAIN

Was the onset sudden or gradual?

Location Localized—diffuse—generalized? Down left arm and up into the jaw? In the back and bones? In the muscles and joints? In the lower limbs? Did it start at the umbilicus and radiate toward McBurney s point? Did it start under the lower right costal border and radiate around to the back and up between the shoulder blades? Was pain felt in the pit of the stomach', radiating straight through to the back?

Severity of Pain Mild or severe? Aggravated by movement breathing pressure? Relieved by food, rest heat vomiting defecation micturition posture movement or any particular medication?

Character Steady—intermittent—sharp—burning—dull ache? Caused by food? What foods? Previous similar episodes?

Associated Symptoms Chills sweating fever, cough vomiting nausea? Treatment given and results of same?

PARALYSIS

Onset sudden or gradual? Follow injury? Nature of injury? Partial paralysis? Complete paralysis? Hemiplegia? One arm and opposite leg? Involuntary bowel and bladder movements? Rational? Comfortable? Irritable—turns away from the light? Comatose? Understands the spoken word? Coherent speech? Previous attacks? Where possible get a good history from the relatives Are pupils equal—dilated—constricted—unequal? Do they react to light—accommodation—consensually? Are the eyes rotated inward outward or upward?

DYSPHAGIA

Describe onset fully Duration? Is it increasing? Any previous episodes? Previous instrumentation? How well can patient swallow ordinary foods? Can only liquids be taken? Does the obstruction seem to increase when swallowing liquid or solid food? Any regurgitation? Is food eaten yesterday regurgitated today? Is there bad odor to the regurgitated food? Any history of weight loss lately? What was the last weight? What is the most the patient has weighed in adult life?

SKIN RASH

Was onset sudden or gradual? Any connection with occupational or professional contacts? Any contact with acids, metals oils, drugs, paints hides? Describe the location grouping shape and color of the lesions Are they moist—dry—itching—symmetrical—macular—papular—maculopapular—pustular—hemorrhagic—crusted—on exposed surfaces? Describe their progression from the onset Do they fade or disappear on pressure? Any recent shellfish or seafood eaten? Previous similar ailment? Is there an allergic history to foods drugs inhalants epidermals or other contact agents? What medicines have been taken lately? Any new clothes or furs worn lately? Any recent vaccinations? Any fever or sore throat? Do any members in the immediate family have a similar rash? Has the patient ever been treated for syphilis? Is there a history of a penile sore—penile ulcer—'haircut — strain —chancre? What does the patient think is the cause of his rash? What treatment has been taken to date and with what results?

SWELLING

Site of swelling? Was onset sudden or gradual? Did it follow trauma? If the result of trauma what was done for it—how soon following the injury, and by whom? If possible describe swelling as to its approximate size The use of nuts, fruits and vegetables for comparisons of size is to be deprecated as no two people have exactly the same idea as to the size of such objects Is the site of swelling painful? Only painful to pressure? If edema is present is it confined to the extremities or

dependent parts? Is it worse at night? Is the swelling markedly decreased in the morning? Is the skin discolored? If the joints are swollen describe them in detail Are they hot, painful to active or passive motion? Are tophi or nodules present? Any previous similar attacks? Does the swelling pulsate? Is it fluctuant? Is pitting edema present? What is the most distressing symptom noted as a result of the swelling? Has the patient ever been treated for heart or kidney trouble? Has he ever taken digitalis, diuretics proprietary medicines such as Harlem oil, or injections? With what results? What other medications have been taken and for how long? Results of such treatment? Is the patient's diet adequate?

COMA OR UNCONSCIOUSNESS

Where possible obtain a history from the family, ambulance driver eye witness friends or police officer Was the onset sudden or gradual? Have there been lucid intervals? Can he be roused? Is there a history of syphilis diabetes, malaria heat stroke, epilepsy or alcoholism? What medications have been taken lately? Is the odor of the breath suggestive? Are the inner or mucosal surfaces of the cheeks burned? Does the patient use sleeping powders, pills or sedatives? Are there any puncture marks on the body to indicate drug injections? Is the tongue burned? Have there been any convulsions chills, or delirium? Are there signs of violence on the body? Is the face flushed pale cyanosed? Describe the character of the pulse and respiration Has there been or is there involuntary passage of feces or urine? Is there any nuchal rigidity? Kernig's sign? Evidence of hemiplegia? Stertorous breathing? Is there any inequality of the pupils? Do they react physiologically? Any paralysis of the arms or legs? Was the patient rational before the onset? Is there any skin rash or petechiae? Are the mucous membranes clear? Is the condition progressively worse unchanged or improved? What treatment has been given and with what results?

GENITO URINARY SYMPTOMS

Has there been or is there any complaint of anuria polyuria oliguria or hematuria? For how long? Associated pain? Radiation of pain? Is the bladder distended? Does patient have trouble starting stream? Is the caliber of the stream smaller than normal? Any urgency, dribbling, or nocturia? Incontinence or eneuresis? Did eneuresis follow a head injury? Is patient dehydrated? What medicines have been taken lately? Any sulfa drugs self administered? Have any catheters or sounds been passed lately? Is there a history of previous gonorrhea or stricture? How was it treated?

VOMITING

Was onset sudden or gradual? Frequency? Retching? Before or after meals? Upon arising in the morning? Amount of vomitus? Does patient vomit at a time when normally the stomach would be empty? Unable to keep anything down? History of recent dietary indiscretion? What foods have been eaten for the previous thirty six hours? History of overindulgence in alcohol? Is there an associated diarrhea, headache or blurring of vision? Does the vomitus contain undigested food, mucus, blood, or bile? Does it contain food eaten several days previously? Is there a history of air sickness or sea sickness? History of many previous similar attacks? What treatment has been given and with what results?

Use of The Printed Case History Form

There is an established place in clinical medicine for the use of the printed case history form Being human, we are fallible and can easily forget or neglect to inquire as to certain leads, which if investigated might well point to the correct diagnosis specific treatment and a consequent early recovery The complete all inclusive history may be of great medico legal importance as it often shows striking discrepancies in later claims of those seeking compensation We do not advocate the use of a case history form as a short cut' There are no short cuts in the practice of medicine especially where diagnosis is concerned The foundation stone of every diagnosis is a careful and thoroughly well organized history and an equally painstaking physical examination

It is quite possible for a patient to have a serious disease and yet present absolutely

nothing in the way of physical findings Early cancer is an example of this, so are the many cases of coronary heart disease It is in these cases that we must rely to the greatest extent upon the history In making a physical examination some physicians are prone to omit several of the most important procedures through what may be termed sheer mental indolence Through such omissions, we often fall into diagnostic errors which are entirely avoidable It should no longer be the case that only a specialist or consultant does a rectal examination Often a trivial deviation from the normal may supply a clue which will lead us to a correct diagnosis

Nearly all physicians follow a pre-arranged schedule or routine in taking a history and making the examination of neurological or psychiatric patients Is it not of equal importance to do likewise in allergic, dermatologic gastrointestinal, and cardiac conditions? Or in low back pain which is so often seen and often poorly treated?

A well organized and all inclusive history and physical examination is of much aid to the pathologist when he reviews a case coming to autopsy or otherwise In records with many entries over a period of years, including successive entries purporting to show progression or improvement it is not uncommon to meet with such statements as 'no change since last entry' no complaints ' or heart and lungs negative' Such records are almost worthless

To those of us who are interested in the statistics of certain cases, their method of treatment and the success or failure of such treatment, the printed form is of especial utility It gives uniformity to the collected material, which then becomes of statistical value

There still exists among many medical men the idea that psychiatry is too complex a specialty to warrant their attempting to acquire a working knowledge of it This point of view is to be deplored, because it is the physician not the specialist who is usually the first to see the mentally disturbed patient There is no reason why the average physician cannot detect deviations from the normal A well planned and organized case history and physical examination form can be invaluable in such cases

Samples of forms used and devised by the author follow in this and other chapters It is hoped that those who use them will modify them to their own needs and points of view It is not to be presumed that the busy practitioner will follow the outlines in every case By practicing with a history outline for varying lengths of time, it is possible to develop a technic of history taking which by skillfully guiding the conversation will direct and restrain a loquacious patient, put the apprehensive person at ease cause a reticent person to expand and will finally secure a history that includes all the data necessary to making the diagnosis yet entails the least possible expenditure of energy on the part of the busy physician

GENERAL MEDICAL HISTORY AND PHYSICAL EXAMINATION—MASTER FORM

Name *Address* *Age* *Sex* S M W D

Occupation *Nationality* *Date* *Ref*

Chief Complaint

Present Illness

Past History Place of birth Health of mother during pregnancy
During infancy and childhood Age of dentition Walking
Talking Any sleeping nursing feeding difficulties
Residence in other cities or countries (give dates)

Past Diseases Measles Mumps Pertussis Chickenpox Smallpox Diphtheria
Scarlet fever Sinusitis Tonsillitis Chorea Rheumatic fever Rheumatism
Influenza Pneumonia Pleurisy Malaria Typhoid
TB exposure Poliomyelitis Encephalitis Meningitis
Hay fever Asthma Urticaria Arthritis Epilepsy Stroke
Diabetes Treated with diet Insulin How much
Cardiac Angina High blood pressure Convulsions
Syphilis Date discovered Chancre Routine blood test Other How much treatment Date last treatment Spinal fluid Results of last blood serologic test
Gonorrhea Treatment Recurrence

Traumatic History Surgery Complications
Accidents—broken bones Complications

Receiving compensation for injuries Any lawsuits pending

Symptom Review Loss of memory Concentration power Personality change
Disturbance in speech Fever Chills Faintness

Head Headache *Aggravated by* *Relieved by* Frequency Duration Projectile vomiting Vertigo Treatment Results
Eyes Failing vision How long Pain Diplopia Spots before eyes Glasses worn Changed Night blindness Treatment

Ears Hearing Tinnitus Pain Discharge Treatment Results
Nose Epistaxis Discharge Head colds Obstruction Treatment Results
Mouth Sore tongue Sore gums Tonsils Sore throat Hoarseness Teeth Recent extractions for Treatment
Neck Swellings Glands removed Stiffness—rigidity

Cardio Respiratory Chest pain
Palpitation Dyspnea Mild—Moderate—Marked exertion
Anginal pain on effort Relieved by First occurred
Orthopnea Relieved by First occurred
Edema of ankles Edema of eyes Progressive?
Cough Productive—Non productive—Blood streaked—Foul sputum
Hemoptysis Night sweats How long Weight loss
Chest pain aggravated by breathing Last x ray of chest
Treatment (Digitalis—Aminophyllin—Diet—Rest—Pneumothorax—Physiotherapy—Other)

Gastro Intestinal Appetite Eating habits
Nausea A M—P M Vomiting A M—P M Post prandial Water brash
Regurgitation Progressive loss of appetite
Anorexia Gas Belching How often
Pain Location
Relieved by food Heat Rest Posture Defecation
Aggravated by food Raw apples Fats Raw vegetables
Pork Meat Radiates to Awakens patient in night
Pain steady—Burning—Colicky—Dull—Aching—Intermittent—Sharp Duration
Hematemesis
Icterus Onset With pruritus With colic
Diarrhea Onset Bloody—Watery—Painful—Well formed—Tenesmus—Cramps
Stool contains Undigested food—Worms—Much gas—Blood (dark—bright) mucus
Frequency Color Black—tarry—Clay colored
Any unusual food eaten lately *Others ill?*
History of travel in tropics Amebiasis Dysentery

Constipation Alternate with diarrhea Duration
Habitual user of cathartics
Hemorrhoids Peculiar diet
Previous X Ray or barium study
Previous treatment
Results

Genito Urinary Polydypsia Polyuria Anuria Oliguria Color
Hematuria Pain Radiates to
Stone passed Medication
Burning Retention Incontinence Enuresis
Stricture Instrumentation
Calibre of stream Dribbling Frequency Urgency
Nocturia For how long Progressive
Previous cystoscopy—pyelography studies with results
Any previous sulfonamides Reactions

Catamenia Age at first appearance Date last period Normal last period
Regularity Duration Amount Pain—nervousness
Leukorrhea Abnormality of menses
Previous treatment
Spotting One child sterility

Sexual life Childhood interest Age of puberty Reaction to puberty
Reaction to marriage—Sex act—Childbirth
Moderate—Excess relations Aversion to sex act
Auto-erotic reactions Hetero-sexual relationships

Skin Pigmentations Onset Location Course
Allergic history to foods inhalants cosmetics drugs industrial contacts

Rashes Onset Location
Fade on pressure Moist Dry Itching Worse at night
Vaccinations lately Fever and sore throat Course
Medicines taken lately

Extremities Pain
Relieved by Aggravated by
Traumatic history
Limitation of motion (in degrees or %)
Causative factor or previous diagnosis
Previous x ray studies
Edema of extremities Worse at night Treatment
Previous bone joint muscle periosteal disease
Results of treatment

Neuromuscular Anesthesia Paresthesia
Ataxia Twitching Girdle pain
Atrophy Lightning pains Tics Athetosis
Paralysis
Describe above fully

Intellectual and Social Development School history
Interests Ability to adjust
Hobbies Interest in church Estimated I Q

Occupational History Kinds of work undertaken

Length of time in various positions

Efficiency Wages earned Per cent of wages saved
Reasons for change in employment
Relation of occupation to disease

Habits Temperate—Moderate—Total abstainer—Intemperate (Periodic—Steady)—Beer—Whiskey—Wine—Rum
D T's Last attack Amounts daily
Hallucinatory episodes Ideas of jealousy Home life
Drugs Morphine Bromides Sulfonamides
Hair dyes Aspirin Barbiturates
Marihuana (Muggles—reefers) Antacids
Headache tablets Quinine
Arsenicals Hormones
Vitamins Insulin
Dietary Coffee cups daily Tea cups daily Milk glasses daily
Usual diet
Peculiarities
Eat between meals Eat fast Slow Largest meal of day
Tobacco Moderate—Heavy—Chain smoker How much daily
Sleep Regularity Hours nightly Insomnia
Relieved by Dreams Nocturnal convulsions

Environmental Location and type of home
Overcrowding Live with in laws Heating adequate Sanitary
Water supply Domestic animals—Pets—Insects

Marital History Age and date of marriage Compatibility
Abortions Miscarriages Financial stress
Health and age of children

Health of spouse

Family History Parents Grandparents
Brothers and sisters
History of Cancer Diabetes Tuberculosis Hemophilia Anemia
Jaundice Arthritis Asthma Hay fever Heart disease
Paralysis Epilepsy Suicides Mental Nervous Alcohol
Syphilis
Other

PHYSICAL EXAMINATION

Development Nutrition Position assumed Mental state
Station Stance Gait Habitus

Skull Symmetrical Exostoses or irregularities Tenderness Scars Hair distribution Alopecia Color hair

Face Symmetrical Abnormal facies Expression Scars

Eyes Pupils reaction to light Accom Consensual Ptosis
Regularity of pupils Sclerae Conjunctiva
Cornea Photophobia Lacrimation Lid lag
Lids Exophthalmos Enophthalmos Glasses
Vision O D /20 O S /20 Jaeger 1 O D O S
Color vision (Ishahara or Pseudo isochromatic plates) green—red blind
Ophthalmoscopic examination
Visual fields

Ears Deformity Mastoid tenderness Drums Canals
External otitis Otitis media Tophi Discharge
Otoscopic examination
Watch heard at cm R cm L Audiometric examination
Audiometric tone loss
Tuning fork

Mouth Color lips Fissures Ulcerations Herpes
Breath Pigmentation Uvula Palate
Gums Bleeding Recession Hypertrophy Lead bismuth line

Teeth Dental hygiene poor—fair—good Dentures worn upper—lower—both Caries Pyor rheal alveolaris Fillings Edentulous
Tongue Coat Dry moist Tremor Protrudes to R—L Geographic
Tonsils Removed—Hypertrophied—Atrophic—Inflamed—Cryptic—Follicular—Exudate
Pharynx Color of postoperative wall Post nasal drip Gag reflex
Larynx Hoarseness Laryngoscopic examination

Neck Adenopathy
Thyroid gland Pulsations
Deviation of trachea Limitation of Flexion—Extension—Rotation

Thorax Symmetry Habitus
Expansion Lag Splinting
Shape A P diameter Rate respiration
Depth respiration Character of respiration
Abnormal pulsations Gross deformity
Breast

Heart Maximal apical impulse in interspace at line
Percussion findings
Palpation
Inspection
Sounds Apex Aortic Pulmonic Tricuspid Murmurs
1st *Systolic*
2nd Erect
3rd Recumbent
Friction rub Thrill *Diastolic*
Rhythm Apical thrust Erect
Extrasystole Auscultatory gap Recumbent
Artery walls compressible Pulse form
Describe murmur

Blood pressure Systolic Diastolic

Lungs Resonance Tactile fremitus
Suppression of breath sounds
Splinting or lag Myoidema
Kronig's isthmus Clavicle percussion
Area of dullness

Apices
Bases
Adventitious sounds
Amphoric breathing Rise of diaphragm
Pleural rub Fluid level

Abdomen Shape Symmetry Pulsations
Tenderness Mass
Spasm Rigidity
Resonance Fluid dullness
Herniae
Ascite Reflexes
Distension Borborygmus Visible peristalsis

Liver Size Edge felt Fingers below costal margin Nodular—tender

Gall Bladder Palpable Tender Murphy's sign

Spleen Enlarged Tender

Kidneys Palpable Movable
Costovertebral tenderness

Genitalia Normal male—female Not examined Epispadias Hypospadias
Redundant prepuce
Penile lesion
Vulvar lesion
Scrotum Epididymis Inguinal glands
Findings of pelvic examination

Varicocele Hydrocele Undescended testicle

Rectal examination Sphincter tone Hemorrhoids Internal—External
Fissure Fistula in ano
Prostate Size 1 2 3 4 Tenderness 0 1 2 3 4 Consistency
Nodules felt Remarks
Results of proctoscopic examination

Lymphatic Glands Neck Axillae Inguinal Epitrochlear

Bones—Spine Scoliosis Kyphosis Lordosis Other
Rigidity Tenderness
Exostoses Deformity

Arms Involuntary movements Wasting Tremor Nails Club fingers
Athetosis Deformity Paralysis—Other *F to F* *F to N*
Reflexes Biceps Triceps Radial periosteal Hoffman

Legs Varicosities Scars Ulcers Deformities Knee jerks
Achilles Plantar Babinski Ankle clonus Kernig Romberg
Vibratory sense Position sense H to K

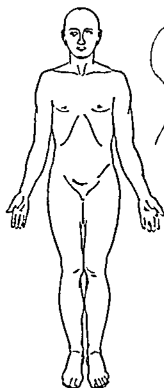
Skin Rash Petechiae Tattoo
Distribution
Sensation disturbances

Summary of Findings

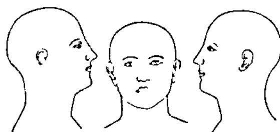
Diagnosis

REFERENCE

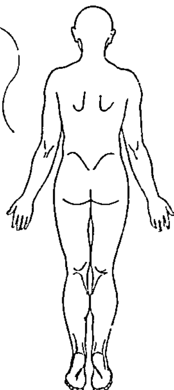
1 Major R H Diagnosing Diseases without Instruments of Precision Jour Kansas Med Society 40 408 1939



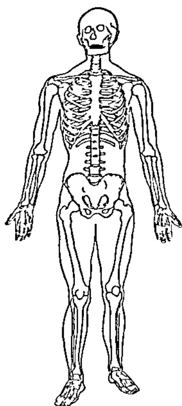
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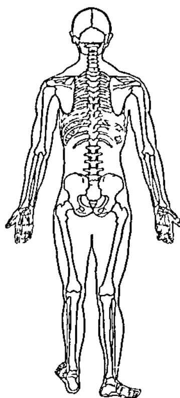
E



C



A



D

Chapter II

NUTRITION AND VITAMIN DEFICIENCY DISEASES

Case Study of Nutritional Deficiency

The correct diagnosis of nutritional deficiency cannot usually be made without a full clinical study, for many of the manifestations of the deficiency are not in themselves diagnostic but are significant only when considered in relation to other findings. Structural changes are not present as a rule until the deficiency is well advanced and, when once established they are to a great extent irreversible. It therefore becomes essential to make the diagnosis before structural changes have occurred. For those especially interested in a detailed study of nutritional deficiencies the following case record form may be of some value.

Name *M* *S* *W* *D* *Sex* *Race* *Age* *Occupation*

Diet Quality Quantity Adequate Inadequate
Recent alteration (Explain)
Meat Dairy foods Fruit Fresh vegetables
Canned foods (What and how often) Home cooked—restaurant meals
Amount spent daily for food Amount spent for liquor
How many people fed on above budget? For how long?

Family History Any malnutrition in other members of the family?
Diabetes Cancer Anemia Gastric ulcer Alcoholism
Nervousness Drug addiction Other
Locale of residences in the past ten years

General Health Well being Able to work Forced to give up work
Lassitude Fatigue Exhaustion Weight loss or gain
Recent illness Operations
Medications taken Results
Fevers Pregnancies

System Review Muscle pain following exercise Pains in extremities
Describe fully
Night blindness Glare blindness Gritty sensation in eyes Palpitation
Dyspnea Edema of legs Plantar pains
Describe fully
Anorexia Sore tongue Dysphagia Diarrhea Epigastric pain
Constipation Numbness Parasthesias Difficulty in walking (describe)
Other
Describe fully

Physical Examination
Skin Loose Thin Edema (dependent or widespread) Dryness Shiny Fissuring Hyperkeratotic plugs Hypohidrosis Hyperkeratosis Pigmentation
Erythema Glove or stocking distribution Exposed surfaces involved Petechiae
Jaundice Ecchymoses *Dermatitis* Perianal Scrotal Labial Beneath breasts
Elbows Knees Hips Other areas
Desquamation Scaly Branny Greasy Mosaic pattern Other
Hair Distribution Overgrowth on trunk Face Elsewhere
Nails Spoon shaped Brittle Lined Other
Skeletal Deformities (Describe fully)

Muscles Tetany Tenderness in muscles after exercise Atrophy
Eyes Palpebral conjunctivae Frost glass appearance over scleral conjunctivae Keratitis
Hippus Nystagmus Fundus

Mouth Pallor of lips Fissuring Angular stomatitis Cheilosis
Tongue Red Swollen Painful Beefy Loss of papillae Smooth Pale Flabby Atrophic Tremor Coated Dry Moist
Teeth Edentulous Occlusion Loose Bleeding gums Dentures Oral hygiene
Respiratory System Laryngeal spasm Other
Cardiovascular Tachycardia Dilatation Edema Peripheral vasodilatation Murmurs Blood pressure Circulation time
Abdomen Ascites Palpable liver edge Palpable spleen Masses Tenderness Rigidity Paralysis Other
Nervous System I *Mental* Apathy Lassitude Spiritual resignation Loss of ambition Anxiety Amentia Restlessness Delusions Stupor Disorientation Confabulation Delirium tremens Other
II *Cranial Nerves* Nystagmus Ocular paralyses Other
III *Motor-Sensory* Loss of ankle jerks Knee jerks Tendon reflexes Hyperesthesias (Plantar skin) Hypesthesias Hypalgesia Position sense Vibration sense Calf tenderness Babinski Other

Laboratory Studies Blood R B C W B C Hb (grams) Smear
Urine Color Reaction S G Sugar Alb Micro
Gastric contents Gastroscopy findings
Sed rate N P N A/G ratio Creatinine Stool fat
Roentgen studies
Glucose tolerance B M R E K G
Proctoscopy findings
Plasma ascorbic acid Serum calcium Serum phosphatase Serum phosphorus Blood pyruvic acid Prothrombin time *Cell* volume Riboflavin (urine)

Summary of Significant Findings

Introduction

A deficiency in any of the dietary essentials of life may result in serious disorders to growth maintenance and development These dietary essentials are calories proteins, calcium phosphorus iron iodine, and the vitamins (A and D thiamine riboflavin nicotinic acid and ascorbic acid) In addition to these factors there are other important substances which are ordinarily supplied by many foods in sufficient quantity They are (1) the essential fatty acids (2) inorganic elements such as sodium potassium, magnesium and chlorine, (3) other substances such as choline biotin pantothenic acid pyridoxine and alpha tocopherol (Vitamin E) and vitamin K which is best considered as a therapeutic agent rather than as a food substance

The ingestion of an insufficient quantity of liquids (1 to 2 liters daily) severe vomiting diarrhea or sweating may result in anhydremia *Protein intake* must be sufficient to provide the necessary amino acids and nitrogen so vital for growth and repair The daily ingestion of at least 50 grams of protein will insure the individual remaining in nitrogen balance Where there is no need to restrict the protein intake it is a good rule to allow 1 gram of protein for each kilogram of body weight (the ideal weight) for adults 1 5 gram per kilo of body weight is allowed in the case of children for the twenty four hour period Lack of protein will give rise to anemia weakness, cachexia and edema in addition to a negative nitrogen balance The number of grams of *carbohydrate* required in the diet can be estimated by multiplying the number of grams of protein by 3 5 The number of grams of *fat* required can be determined by dividing by 9 (caloric value of fat) the number of calories remaining after the number supplied by protein and carbohydrate (multiply the grams of each by 4 the caloric value of carbohydrate and protein) has been deducted from the total caloric value of the diet *Minerals vitamins* and *bulk* are supplied by including in the diet at least 500 grams of vegetables (one a leafy variety) and fruits, 500 c c of milk 60 grams of meat at least one egg and 30 grams of butter

Caloric Requirements

McLester (1) doubts if under ordinary circumstances a man's caloric requirements can be estimated closer than 500 calories per day, or his protein requirements in steps smaller than 20 grams It is safe to assume that the average American man or woman leading a quiet life with little or no exercise requires about 2000 calories If he has a sedentary occupation 2500 calories will suffice, if he has light work, he can get along on 3000 calories if on moderate work 3500 calories, and if he is doing hard labor 4500 calories or more are necessary

FOODS AS SOURCES OF NUTRIENTS

Vitamin A

Vitamin A is found in milk and dairy products, beef liver, fat, and certain vegetables Vitamin A and carotene are stable to heat and are therefore not diminished by cooking or canning The green leafy and yellow vegetables are the most outstanding sources of vitamin A Examples of these are beet tops, chard, kale, mustard greens spinach turnip greens, carrots, squash and sweet potatoes Butter, milk and eggs are important sources also

Vitamin B_1 or Thiamine

Pork is an outstanding source of thiamine One serving will supply almost the daily requirement or 1 8 milligrams Thiamine is obtained in small quantities from a number of foods Examples are found in the table below

Foods	Amount of Thiamine
Lamb—1 portion	0 27 mg
Beef or veal—1 portion	0 17 mg
Whole wheat bread—4 slices	0 4 mg
Enriched bread—4 slices	0 3 mg
Milk—1 pint	0 2 mg
Peanuts—1 ounce	0 2 mg
Oatmeal—1 ounce	0 2 mg

Vitamin B_2 or Riboflavin

Milk is an important source of riboflavin and one pint will supply about one third of the daily requirement A serving of meat will supply about one-twelfth of the daily requirement A four ounce serving of liver supplies about 3 mg of riboflavin Milk which is allowed to stand in the light will lose a considerable portion of its riboflavin content

Nicotinic Acid or Niacin

Liver is a rich source of niacin A four ounce portion of liver contains more than the daily requirement of 18 mg A serving of red meat provides from 7 to 10 mg Bran and whole grain cereals are good sources of niacin

Ascorbic Acid

There are many sources of vitamin C as can be seen from the following list

Foods	Amount of Ascorbic Acid
One half grapefruit	75 mg *
Strawberries	75 mg
One half cantaloupe	60 mg
Raw cabbage—2 ounces	40 mg
Sweet potatoes—four ounce serving	30 mg
Baked potato—five ounce serving	25 mg
Orange juice—four ounce serving	60 mg
Tomato juice—four ounces	24 mg

Other sources Pears apples peaches bananas watermelon turnips and lettuce

* Full daily requirement

Protein

Meat and milk products are the best source of protein No single food in ordinary quantities supplies the daily requirements A serving of meat fish or fowl contains about 25 grams of protein four ounces of bread and a pint of milk will add an additional 10 grams each Soy bean milk is an excellent source of protein Little protein is supplied by vegetables

Calcium

The intake of calcium is likely to be more deficient in the average American diet than any other substance particularly if milk does not form a part of the diet There are few good sources of calcium other than milk It has been shown that to obtain calcium equilibrium it is necessary to take from 0 4 to 0 5 gm of calcium each day and the average dietary exclusive of milk and cheese will be about 0 3 gm or less A person on such a calcium intake therefore develops a negative balance Calcium is withdrawn from the bones Next to milk and cheese the best sources of calcium

are turnip greens, mustard greens, collards, kale, broccoli and cauliflower. Four ounces supply about 0.2 grams of calcium. The use of cream soups, desserts and ice cream should

TABLE I

Recommended Dietary Allowances

Committee on Foods and Nutrition, National Research Council

	Calories	Protein	Calcium	Iron	Vitamin A†	Thiamin (B_1)	Riboflavin	Nicotinic Acid	Ascorbic Acid	Vitamin D
		gm	gm	mg	I U	mg ‡	mg	mg	mg	I U
Man (70 kg.)										
Moderately active	3,000	70	0.8	12	5,000	1.8	2.7	18	75	††
Very active	4,500					2.3	3.3	23		
Sedentary	2,500					1.5	2.2	15		
Woman (56 kg.)										
Moderately active	2,500	60	0.8	12	5,000	1.5	2.2	15	70	††
Very active	3,000					1.8	2.7	18		
Sedentary	2,100					1.2	1.8	12		
Pregnancy (latter half)	2,500	85	1.5	15	6,000	1.8	2.5	18	100	400–800
Lactation	3,000	100	2.0	15	8,000	2.3	3.0	23	150	400–800
Children up to 12 years										
Under 1 year§	100/kg	3½ kg	1.0	6	1,500	0.4	0.6	4	30	400–800
1–3 years	1,200	40	1.0	7	2,000	0.6	0.9	6	35	††
4–6 years	1,600	50	1.0	8	2,500	0.8	1.2	8	50	
7–9 years	2,000	60	1.0	10	3,500	1.0	1.5	10	60	
10–12 years	2,500	70	1.0	12	4,500	1.2	1.8	12	75	
Children over 12 years										
Girls 13–15 years	2,800	80	1.3	15	5,000	1.4	2.0	14	80	††
16–20 years	2,400	75	1.0	15	5,000	1.2	1.8	12	80	
Boys 13–15 years	3,200	85	1.4	15	5,000	1.6	2.4	16	90	††
16–20 years	3,800	100	1.4	15	6,000	2.0	3.0	20	100	

Tentative goal toward which to aim in planning practical dietaries; can be met by a good diet of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

† Requirements may be less if provided as vitamin A, greater if provided chiefly as the pro-vitamin carotene.

‡ 1 mg. thiamin equals 333 I.U.; 1 mg. ascorbic acid equals 20 I.U.

§ Needs of infants increase from month to month. The amounts given are for approximately 6–8 months. The amounts of protein and calcium needed are less if derived from breast milk.

Allowances are based on needs for the middle year in each group (as 2, 5, 8, etc.) and for moderate activity.

†† Vitamin D is undoubtedly necessary for older children and adults. When not available from sunshine, it should be provided, probably up to the minimum amounts recommended for infants.

Further Recommendations Adopted 1942

1. The requirement for vitamin K is usually satisfied by any good diet. Special consideration needs to be given to newborn infants. Physicians commonly give vitamin K either to the mother during pregnancy or to the infants immediately after birth.

2. The requirement for iodine is small, probably about 0.002 to 0.004 milligram a day for each kilogram of body weight. This amounts to about 0.15 to 0.30 milligram daily for the adult. This need is easily met by the regular use of iodized salt; its use is especially important in adolescence and pregnancy.

3. The requirement for copper for adults is in the neighborhood of 1.0 to 2.0 milligrams a day. Infants and children require approximately 0.05 per kilogram of body weight. The requirement for copper is approximately one tenth of that for iron.

Copies of "Recommended Dietary Allowances" are available on request from the Nutrition Division, Office of Defense Health and Welfare Services, Federal Security Agency, 601 Pennsylvania Avenue, N.W., Washington, D.C.

of hot biscuits, made with self-rising flour which contains calcium acid phosphate, will be encouraged for those who have a distaste for milk.

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Pathology of the Kidney and Adrenal Gland in Relationship to Hypertension*

SHELDON C SOMMERS

Boston University School of Medicine

Prolonged hypertension damages the kidneys resulting in renal parenchymal atrophy and arteriolar nephrosclerosis as well as variable degrees of renal arteriosclerosis and pyelonephritis The adrenal weights are often increased but not to a statistically significant degree and periadrenal arteriolar sclerosis is present These classic morphologic indications of chronic hypertensive disease at autopsy are representative of later stages in the natural history of untreated or uncontrolled high blood pressure In the present review the surgical pathology of renal and adrenal tissues from living hypertensive persons will be considered instead of findings exemplified by a grossly contracted finely granular kidney and a correspondingly advanced microscopic nephrosclerosis

Advantage is taken of the abundant surgical material collected at the Massachusetts Memorial Hospitals largely by Dr Reginald H Smithwick and associates in the period between January 1 1946 and November 15 1958 Included in the over all analysis were 318 nephrectomy specimens not necessarily from hypertensive patients 1970 kidney biopsies mostly obtained at the time of sympathectomy for hypertension from 1430 patients and 97 adrenalectomy specimens removed in the treatment of hypertension All of the pathologic material has been reexamined without prior knowledge of the patients names clinical status or diagnoses and later has been correlated clinicopathologically as reported in part elsewhere [1 3]

ARTERIOLAR NEPHROSCLEROSIS

Approximately 83 per cent of the cases with renal biopsies showed a pure arteriolar sclerosis with or without secondary renal parenchymal lesions findings that are characteristic of essential hypertension [4] The biopsies were from individuals selected as candidates for surgical therapy and thus likely

The research projects reviewed were supported by grants from the Massachusetts Heart Association the American Heart Association and the Smithwick Foundation

represented relatively more serious clinical hypertension in patients perhaps younger and probably in better general physical condition than many persons found in the universe of hypertensive disease The renal biopsies were obtained at surgery under direct observation measured about 12 x 5 x 4 mm and were composed almost wholly of kidney cortex Alterations found would necessarily be those that were fairly diffuse in the cortex and not restricted to the kidney medullary or hilar structures

In support of earlier reports by Castleman and Smithwick,[5, 6] a minority of the renal biopsies approximately 1 6 per cent had no arteriolar or other lesions identified and were within normal limits by histopathologic criteria

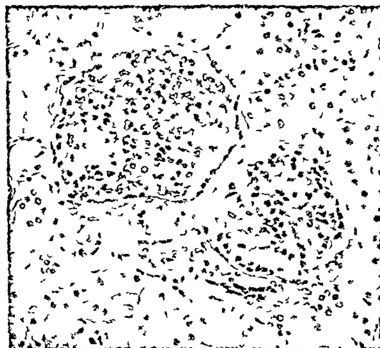


Fig 1 Biopsy of kidney from a hypertensive patient without apparent arteriolar disease The afferent arterioles in the center appear to be contracted in spasm and the adjacent proximal convoluted tubules show cloudy swelling Hematoxylin and eosin, × 200

Enough such cases were observed to indicate that hypertension can antedate arteriolar nephrosclerosis and that in this respect the kidney is the victim of the elevated blood pressure[7] It is not implied that an established arteriolar nephrosclerosis plays no role in maintaining or elevating the blood pressure level and evidence for a renal effect in perpetuating or enhancing a preexistent hypertension is presented later

The earliest renal parenchymal alteration discerned was parenchymatous degeneration (also termed cloudy swelling) in the epithelium of the proximal convoluted tubules This change is banal reversible and significant only because the biopsies were fixed immediately in the operating room and because other histologic details were usually nicely demonstrated. In affected tubules the cytoplasm was swollen, with bulging of the free cell

surfaces into the tubular lumens and the mitochondrial rods were fragmented into minute granules Tubular lumens were from slightly to rather widely dilated as Shorr[8] remarked and sometimes the tubular epithelium had undergone both cytoplasmic shrinkage and cloudy swelling Such degenerative changes occurred in about half of the specimens without or with only slight arteriolar thickenings In instances with more advanced arteriolar sclerosis about 80 per cent had convoluted tubular cloudy swelling or atrophy These represented the most common parenchymal alterations found in the biopsies with pure arteriolar sclerosis

Histochemical study by J F A McManus[9] of some of these biopsies from



Fig 2 Moderate arteriolar nephrosclerosis (grade II) is evident with thickening and hyalinization of the arteriolar wall Some interstitial fibrosis and degenerative alterations of convoluted tubules are also shown Hematoxylin and eosin × 200

hypertensive persons without evident arteriolar lesions showed indications of an ischemic type of alteration of the glomerular structure

Experimentally produced ischemia in animals kidneys ordinarily after clamping or ligatures left in place for 6 10 45 or 60 minutes has been recorded several times as producing mitochondrial fragmentation or cloudy swelling and dilatation of the convoluted tubules predominantly the proximal segments[10,11] It is evidently a nonspecific response to anoxia, reversible at stages short of necrobiosis tubulorrhexis or necrosis In recent experiments on young animals a comparable convoluted renal tubular dilatation and cloudy swelling developed after vagotomy This could indicate a relative predominance of sympathetic nervous stimuli[14]

Spastic contraction of the small arterioles afferent to glomeruli was the earliest vascular alteration found Cautious coworkers and friendly critics

have doubted that arteriolar spasm can be positively identified in fixed specimens by histopathologic study While this may be so the presence of unusually concentrically overlapped myofibrils and nuclei around an arteriolar lumen so narrowed that one squeezed erythrocyte fills almost the entire space has been considered as spastic contraction in the absence of any visible structural abnormality (Fig 1) This appearance of spastic arterioles is rarely seen in surgical pathologic specimens of many tissues including kidney biopsies or specimens of uterine cervix from normotensive persons or in sympathetic nerve chains and adjacent areolar tissues from hypertensives

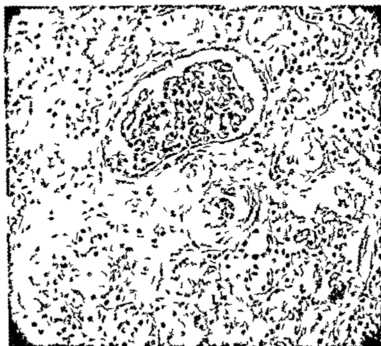


Fig 3 Severe arteriolar sclerosis (grade III) has resulted in nearly complete occlusion of two small arterioles by thickening and degenerative changes in vessel walls The glomerulus and Bowman s capsule are altered because of ischemia Hematoxylin and eosin × 200

The experimental hypertension that accompanies adrenal regeneration in rats likewise is considered to precede the development of lesions of arteriolar nephrosclerosis according to Skelton [13]

Arteriolar sclerosis in surgically obtained kidney specimens is at first typically focal and irregular in its localization and in fact is uniform in extent and degree only in the most severe and advanced stages Sometimes arterioles that are nearly normal are so inconspicuous that an unusually long time must be spent in locating them Abnormal thickenings of the renal arteriolar walls occur predominantly in the small arterioles afferent to glomeruli first relatively close to the glomerular roots The larger renal arterioles and small arteries typically appear stretched wide and are relatively dilated until sclerosis of small arterioles is well advanced No abnor

mality of efferent arterioles was found and efferent arteriolar sclerosis has been claimed as restricted to the diabetic kidney [15] Glomerular and inter tubular capillaries were altered apparently only secondary to arteriolar sclerosis Venules and collecting cortical veins were characteristically di lated and engorged with blood For this there is no adequate explanation at present although partial venous paralysis muscular sphincters at the kidney hilus relative stagnation of venous drainage or splanchnic congestion might be implicated [7]

The synthetic developmental stages of arteriolar sclerosis included spas tic contraction intramural edema muscular hypertrophy and finally de generation with a pooling of the ground substance basement membrane fragmented elastica and muscular tissue into an irregular amalgam some times associated with a deposition of fibrocollagenous foci (Figs 2 3) It is uncertain whether the process regularly proceeds in the same sequential steps and why it is focally more or less severe and quite variable both in the quantity and quality of pathologic alterations Arteriolar sclerosis was graded as I II and III for all kidney material based upon a successively more severe thickening and degeneration of the vessel walls and a conse quent narrowing of their lumens In each biopsy this referred to the average degree of sclerosis throughout the specimen obviously involving some compromise [7] However this grading has a statistically valid clinical signifi cance noted below When one patient had bilateral kidney biopsies with different grades of arteriolar sclerosis the case was listed as of grade 0 I or II III etc (Table 1)

When the findings were analyzed in relation to the grades of arteriolar sclerosis the more advanced degrees of renal parenchymal atrophy stromal fibrosis and evidences of degeneration accompanied the more severe grades of vascular disease as has been frequently reported However fibrinoid necrosis of renal arterioles traditionally the indication at autopsy of a clinically malignant hypertension did not have an equal significance in surgical material By fibrinoid necrosis is meant a smudgy degenerative alteration of a part or all of an arteriolar wall stringy in character and staining rather like fibrin In the material studied its appearance its locali zation in vessel walls and relation to their lumens favored an imbibition of

TABLE 1 PATHOLOGIC DIAGNOSES AND GRADES OF ARTERIOLAR NEPHROSCLEROSIS FROM KIDNEY BIOPSIES OF 1430 PERSONS WITH HYPERTENSION

KIDNEY	CASES*
Negative	17
Negative–Grade I	7
Grade I	299
Grade I–II	120
Grade II	694
Grade II–III	34
Grade III	55
Negative–Grade II	1
Grade I–III	3
Pyelonephritis	211
Unilateral Disease	19
Glomerulonephritis	10

* Total biopsies 1848

plasma into the vessel wall followed by coagulation of fibrin with a subsequent partial enzymatic hydrolysis to yield fibrinoid. As such fibrinoid necrosis seemed to reflect sudden or local exacerbations of intravascular pressure or both that tended to force blood constituents into a vessel wall at places where it was doubtless not wholly normal. Fibrinoid arteriolar necrosis occurred focally in cases with all grades of arteriolar sclerosis and was neither restricted to nor characteristic of grade III sclerosis.[7] Incidentally clinicopathologic study did not support fibrinoid necrosis in renal biopsy material as necessarily indicative either of a clinically malignant uremic or terminal condition, with the important proviso that something definitive was done therapeutically.[1]

At all grades of arteriolar sclerosis short of the most severe the process of vascular thickening both in type and extent would permit some reversibility or arteriolar redilatation provided that adequate therapy was administered. In the cases analyzed clinicopathologically the post sympathectomy survivals were equally favorable for all grades of arteriolar sclerosis except grade III. Fibrinoid arteriolar necrosis did not noticeably alter the prognosis.[1]

Glomerular and juxtaglomerular apparatus alterations were not very striking in this material. With ischemia secondary to local efferent arteriolar narrowings the glomerular walls became slightly stiffened and the whole capillary net appeared simplified and eventually sagged collapsed and hyalinized in some individual glomeruli. While a majority of kidneys with more advanced arteriolar sclerosis had some completely hyalinized glomeruli, these only uncommonly exceeded 10 per cent of the total counted.[7] Glomeruli from arteriolar nephrosclerosis have an increased ultraviolet absorption at shorter wave lengths apparently reflecting increased amounts of inorganic cations. Juxtaglomerular cells were considered either normal or swollen and degranulated and they were strikingly altered only in a few cases. Currently the counting method and special stains of the Hartrofts[16] are being applied to some of the material in an attempt to study more carefully this aspect of hypertension.

Stromal scars microscopically with or without intermingled foci of lymphocytes were believed to reflect the parenchymal atrophy and shrinkage that result in the typical gross finely pitted renal cortical appearance in hypertension. Scars and locally advanced arteriolar sclerosis were associated architecturally in a way that favored slow noninfarctive ischemic degeneration as the most likely responsible factor. Scars and lymphocytes alone do not constitute inflammation in the ordinary sense as is generally accepted by many of the present generation of teachers of pathology.

PYELONEPHRITIS

In about 15 per cent of the kidney biopsies pyelonephritis associated with arteriolar nephrosclerosis was diagnosed (Table 1). Autopsy series have indicated that about 15 to 20 per cent of hypertensives have chronic pyelonephritis.[1, 18] In view of many unsettled problems in the field of pyelonephritis including (a) the role of bacterial and viral agents, (b) the natural history of the process or its subvarieties, (c) the reasons that it may heal or recur, (d) the sites and types of renal damage that correlate best with hypertension, (e) the interplay of inflammation with ischemia, (f) its

relationship with arteriolar nephrosclerosis in a situation where either condition may be primary or cause the greater tissue damage and (g) host factors—either inherited acquired or both—no satisfying generalizations can be made about the frequency or importance of a transient or persistent pyelonephritis in hypertensive persons

Criteria of pyelonephritis in use for the acute process are the presence of pus casts in tubules with or without interstitial neutrophil exudation Chronic pyelonephritis involves a triad of lesions (a) dilated tubules containing colloid casts (b) interstitial scarring and (c) interstitial leukocytes including some plasma cells (Fig 4) Should the criteria be met except that



Fig 4 Renal biopsy with interstitial chronic inflammation and fibrosis atrophy of some renal tubules moderate arteriolar sclerosis and one incompletely atrophied glomerulus exemplifying chronic pyelonephritis with grade II arteriolar sclerosis Hematoxylin and eosin × 200

plasma cells are absent the condition is considered as healed or inactive pyelonephritis Arteriolar sclerosis is graded separately and in most of the available cases it was of moderate severity (grade II)

Exaggerated renal parenchymal and vascular damage and degeneration commonly attend pyelonephritis in hypertensive persons [19] Clinicopathologic studies of diastolic blood pressures when correlated with biopsy findings showed that with each successively higher grade of pure arteriolar nephrosclerosis the average diastolic blood pressure of the group rose to a statistically significant degree Established arteriolar nephrosclerosis and elevated diastolic pressure levels thus had a mathematical relationship probably reflecting a renal factor in established hypertension (Table 2) [21] Grades of arteriolar sclerosis and mean diastolic pressures in pyelonephri

tis were correlated The grade III arteriolar sclerotic group with pyelonephritis had a significantly higher average pressure than either the pyelonephritic groups with grade I or II arteriolar sclerosis Furthermore for the same grade of arteriolar sclerosis the presence of pyelonephritis in each group was associated with a significantly higher average diastolic pressure than was found with pure nephrosclerosis To emphasize the greater clinical severity of hypertension accompanied by pyelonephritis the post sympathectomy survival of this group was on the order of only 60 per cent at 5 years This increased mortality corresponded to that found with severe pure arteriolar sclerosis (grade III) although pyelonephritis rarely had an associated arteriolar thickening of equal severity [2]

TABLE 2 MATHEMATICAL RELATIONSHIP BETWEEN AVERAGE DIASTOLIC BLOOD PRESSURES AND GRADES OF ARTERIOLAR NEPHROSCLEROSIS

ARTERIOLAR SCLEROSIS GRADE	AVERAGE INCREASE OF DIASTOLIC PRESSURE ABOVE NORMAL (90 mm Hg)	
	NO PYELONEPHRITIS	PYELONEPHRITIS
I	10 3 *mm Hg*	21 5 *mm Hg*
II	19 6	25 3
III	32 1	43 4

To determine the average grade of arteriolar nephrosclerosis (x) subtract 90 from average diastolic blood pressure (y) and divide by 10 In case pyelonephritis is present divide by 15 Nearest integer is the desired grade

Example Average blood pressure 170/116 no pyelonephritis $y = 116$ $x = \frac{116\ 90}{10}$ $= 2\ 6$ Nearest integer is 3 therefore x = grade III

From a practical viewpoint, a diagnosis either of arteriolar sclerosis grade III or of pyelonephritis and any grade of arteriolar thickening indicated a less favorable prognosis for post sympathectomy survival in hypertension with only about two-thirds as many 5-year survivors as in the other groups [1, 2] Study is now in progress to compare the various individual renal components and to estimate what parts of the nephron are the most seriously damaged in pyelonephritis with hypertension

UNILATERAL RENAL DISEASE

Hypertension associated with one atrophied, ischemic or otherwise diseased kidney the so called Goldblatt kidney [9] was estimated to occur clinically in about 1 per cent of the present material and nephrectomy usually had been performed Two of the total 19 possible cases examined pathologically were identified retrospectively from bilateral biopsies that differed by two grades of arteriolar nephrosclerosis and they had not undergone nephrectomy [7]

While occasional clearly acceptable cases of the Goldblatt kidney are observed at autopsy the pathologic diagnosis is more difficult in surgical material particularly if no contralateral renal biopsy is provided Lacking a prolonged follow up or any conviction that the procedure necessarily has been followed by a real amelioration of hypertension the pathologist using conventional methods cannot as yet predict how successful any individual nephrectomy may prove In general considerable apparently functionally

adequate kidney tissue is present (Fig 5) By a combined histochemical and histometric analysis an attempt is being made to identify some useful criteria by which a true Goldblatt kidney may be identified morphologically

GLOMERULONEPHRITIS

Approximately 0 5 per cent of the biopsied hypertensive cases treated surgically had both an arteriolar sclerosis and glomerulonephritic lesions apparently two independent conditions affecting the same individual The clinical selection process was successful in excluding all instances of classic

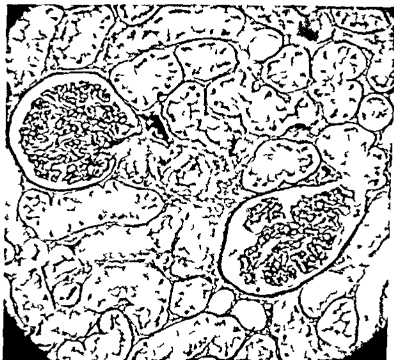


Fig 5 Portion of a nephrectomy specimen from a case with a dramatic postoperative improvement in hypertension No gross vascular abnormality was found pathologically The kidney weighed 106 gm and microscopically had cloudy swelling of the convoluted tubules with focal atrophy and arteriolar sclerosis grade I These changes are demonstrated as well as the unusually enlarged juxtaglomerular apparatus Colloidal iron PAS picric acid stain × 150

proliferative glomerulonephritis and all the biopsied cases had either a membranous inactive or healed glomerulonephritis A definite diffuse acellular thickening of the glomerular capillary walls was the chief diagnostic point Insufficient cases were available for clinicopathologic comparisons The use of open surgical kidney biopsy in difficult medical diagnostic situations had provided over 20 additional examples of glomerulonephritis in whom hypertension was not a constant finding

MISCELLANEOUS

Of all the other conditions involving the kidney or adrenal that may be

accompanied by hypertension only hyperaldosteronism and pheochromocytoma were represented in the surgical material analyzed sufficient together to account for 1 per cent of the cases They are discussed with the adrenal gland

Cushing's syndrome accompanied by hypertension has an identifiable abnormality of the glomerular stromal ultraviolet absorption[23] but the routine pathologic findings are nonspecific and the same is true of the renal lesions resulting from excessive desoxycorticosterone[4] Similarly hypertension with polycystic kidney disease aberrant (pelvic) kidney total nephrectomy diabetic glomerulosclerosis renal periarteritis nodosa renal cell carcinoma etc warrant mention chiefly for completeness in view of their relative rarity in the hypertensive population and the likely predominance of other manifestations of the individual diseases

ADRENALECTOMY SPECIMENS

Adrenal gland tumors were collected from operative material of 97 hypertensive patients Clinical factors largely governed which cases were adrenalectomized and these probably included more severe and complicated situations than the average hypertensive individual would demonstrate The mean weight per adrenal gland was 6 1 ± 2 0 gm which is within the usual normal limits as given in textbooks When the adrenal weight was compared with two series of 220 autopsied cases each of which had or did not have clinical or pathologic evidences of hypertension both autopsied series had heavier average adrenal weights but the differences were not statistically significant[5] Tumors are considered separately

Various workers have argued for or against the existence of a genuine adrenal hypertrophy accompanying hypertension[26] The present series showed no significant weight increase and the factor that tends to cause a minor adrenal weight gain in postmortem material may act only terminally The effect of congestive heart failure in increasing adrenal weight noted by Paul et al[27] may be involved Since the adrenal is a compound gland with a cortex medulla stroma and vessels failure to demonstrate a significant change in its total weight does not exclude an enlargement of some component at the expense of others

Microscopic scrutiny of the adrenal has not been very rewarding in understanding its metabolic and endocrine functions By routine criteria aside from a pericapsular arteriolar sclerosis consonant with that present in kidney biopsies four fifths of the adrenalectomy specimens appeared within normal limits with a lipoid rich cortex and intact medulla Comparison with control adrenal material from normotensive persons showed no statistically significant differences in the thickness of the outer capsule number of extracapsular nodules thickness of the medullary muscular vein walls or abundance of cortical lipoid[5]

Cytometric analysis carried out by Dr J W Goddard uncovered one statistically significant difference in that hypertensive adrenalectomy material had definitely smaller more close packed cells of the adrenocortical zona glomerulosa[5] The work of Deane Shaw and Greep[9] and others indicates that this reflects a relative excess of sodium ions in the intercellular fluids From other types of investigations a similar conclusion has been

drawn concerning individuals with essential hypertension who have an abundant or perhaps excessive intercellular sodium content[29]

Histochemical procedures showed a tendency in hypertension for cortical cells to infiltrate the adrenal medulla and for intracortical nodules to form that were out of phase with the unaffected cortex How frequent or significant such changes are in hypertension is not clear

ADRENAL ADENOMAS

True gross adenomas usually single palpable without internal zonation and with compression of the adjacent uninvolved adrenocortex were found

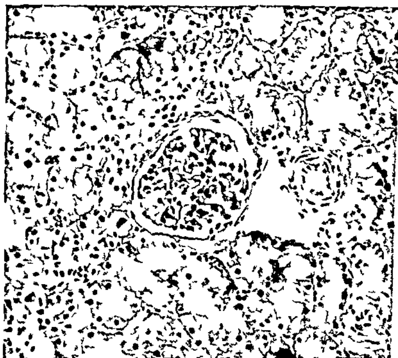


Fig 6 Peculiar vacuolar degeneration in convoluted renal tubules in a patient who had a sympathectomy and an adrenal adenoma removed in 1947 and experienced a remission of hypertension thereafter Laboratory findings are consistent with hyperaldosteronism as the likely cause of this nephropathy Hematoxylin and eosin × 200

in 21 per cent of the adrenalectomy series and also in 20 per cent of a series of 220 autopsied hypertensive persons This is 10 times the expected incidence and the 2 per cent found in a control series of 220 autopsied previously normotensive individuals It is emphasized that the minute multiple zonated noncompressing so-called nodules of adrenocortex were not included or considered as genuine adenomas

Primary hyperaldosteronism was identified clinically in 7 patients who had an adrenalectomy and one additional doubtful case had morphologically normal adrenal glands removed[30] Five of these had adrenocortical adenomas and 2 either unilateral or bilateral adrenocortical hyperplasias One case was recognized retrospectively from the vacuolar degeneration

of the renal convoluted tubular epithelium or so-called hypokalemic ne phropathy (Fig 6)[31] This was not observed in the more recent patients who were operated upon while in better electrolyte balance and their renal biopsies showed only arteriolar nephrosclerosis

The adenomas accompanying hyperaldosteronism measured 1 5 to 3 5 cm in diameter were somewhat flattened and they were not distinguishable from other adrenocortical adenomas by ordinary pathologic criteria either grossly or microscopically (Fig 7) They were soft homogeneous and had a bright orange yellow color Microscopically these adenomas were partly encapsulated and composed of fasciculated cords of cortical cells some unusually swollen with lipoid (Fig 8)



Fig 7 A 1 5 cm adrenocortical adenoma that was associated with primary hyperaldosteronism

In the great majority of cases with adrenocortical adenomas and hyper tension there was no evidence of hyperaldosteronism and it is not known what steroids may have been produced This situation appears fruitful for further research since it apparently applies to about 20 per cent of hyper tensive individuals Removal of the adenomas seemed to have a beneficial effect on the blood pressures and clinical courses of some patients Un identified steroids other than aldosterone secreted by these adrenocortical adenomas perhaps were actually responsible for the hypertension

PHEOCHROMOCYTOMAS

A total of 16 tumors were available from operations and these have re cently been studied pathologically as part of a total series of 107 phe

ochromocytomas reported from the Department of Pathology, Massachusetts Memorial Hospitals by Dr Russell P Sherwin[3] The average tumor weight was 90 gm (Fig 9) Salient findings by Sherwin were that the Henle dichromate reaction on fresh tissue was the most valuable single aid in making a rapid pathologic diagnosis although an occasional pheochromocytoma that secretes mainly norepinephrine may give a negative chromaffin test The tumors were of three main cell types one of which usually was predominant both in the pheochromocytoma and in the adjacent uninvolved adrenal medulla If strict pathologic criteria are used in the histologic diagnosis very few pheochromocytomas will prove to be malignant although these benign adrenal medullary tumors may be multicentric[3]

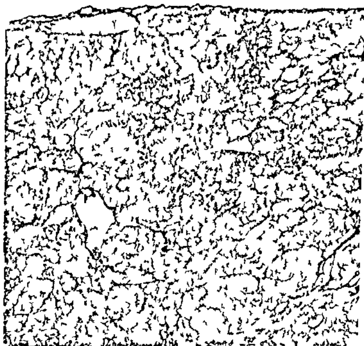


Fig 8 Low power view of an adrenal adenoma from the same case of hyperaldosteronism as illustrated in Fig 6 The fasciculated cords of lipoid rich cortical cells and the compression of adjacent uninvolved adrenal are evident Hematoxylin and eosin × 20

The effect upon renal vessels of the epinephrine and norepinephrine secreted in different proportions by pheochromocytomas is interesting Unlike in essential hypertension where small renal arterioles are the most severely affected with pheochromocytomas the more severe lesions are found in the small renal arteries Unusual subendothelial edema and locally marked intimal proliferations occur in these arteries while the small renal arterioles may appear unaltered or show grade I sclerosis (Fig 10) The renal arterial lesions are not fibrotic and there is usually not an advanced arteriolar nephrosclerosis which helps to account for the frequent postoperative reversion of the blood pressure to normal levels In addition with pheochromocytomas a dilatation of the capillaries at the renal glomerular roots occurs as a fairly distinctive "jet lesion"[3]



Fig 9 Over all view at low magnification of a pheochromocytoma that weighed 20 7 gm to show its relationship to the adrenal medulla central cystic degeneration and the congestion that gave the tumor a reddish color Hematoxylin and eosin $\times$ 8

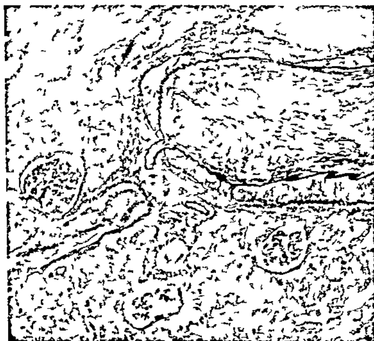


Fig 10 Kidney biopsy from the same case of pheochromocytoma as illustrated in Figure 9 Extreme localized intimal arterial thickening is present but the renal arterioles show only slight sclerosis Verhoeff stain, $\times$ 120

SUMMARY

The surgical pathology of the kidney and adrenal with hypertension has been reviewed utilizing renal biopsies or nephrectomy specimens from 1430 patients and adrenal tissues from 97 patients Pure arteriolar nephrosclerosis accounted for 83 per cent There were no renal vascular lesions in 1 6 per cent of the cases indicating that hypertension precedes nephrosclerosis A convoluted tubular degeneration attributed to renal ischemia was the most common parenchymal alteration found Arteriolar sclerosis was considered to develop in a localized and irregular manner via sequential stages of arteriolar spasm edema muscular hypertrophy and eventual arteriolar de generation occasionally with fibrosis Glomeruli tubules and renal stroma were altered secondary to the ischemia associated with arteriolar disease *Established nephrosclerosis showed a mathematical relation between the* grade of arteriolar thickening and the average diastolic blood pressure indicating that renal factors participate in maintaining a chronic hyper tension

Pyelonephritis was present in 15 per cent of cases with significantly higher average diastolic blood pressures and a less favorable prognosis Fibrinoid renal arteriolar necrosis in surgical material was believed to reflect an exacerbated hypertension and was correlated neither with any particular grade of nephrosclerosis nor with a worse post sympathectomy prognosis Unilateral renal disease and glomerulonephritis accounted together for about 1 5 *per cent of the hypertensive cases*

Adrenal glands in hypertension were morphologically normal in 80 per cent of the cases studied aside from a shrinkage of the zona glomerulosa cells that implied an abundance of sodium ions in interstitial fluid In 20 per cent of cases a genuine adrenocortical adenoma accompanied hyper tension and 5 of 20 excised adenomas were found with hyperaldosteronism Sixteen functional pheochromocytomas were collected Renal biopsy pecu liarities in the hypertension due to hyperaldosteronism or pheochromocytoma are described

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Relationship of Renal Juxtaglomerular Cells to Sodium Intake, Adrenal Cortex and Hypertension*

*PHYLLIS M HARTROFT LEONARD N NEWMARK** and JAMES A PITCOCK****

Washington University School of Medicine

The function of renal juxtaglomerular (JG) cells specialized secretory cells in the wall of the afferent glomerular arteriole is still unknown Goormaghtigh[1 2] discovered they were more numerous and hypergranulated *in renal ischemia both experimentally produced and in man He suggested* these cells might be the source of renin and therefore implicated in development of hypertension Dunihue[3] was the first to find hypergranulation of JG cells in bilaterally adrenalectomized animals Because this change could be prevented or reversed by injections of desoxycorticosterone acetate (DCA) he postulated that a decrease in circulating mineralocorticoids stimulated JG cells But another important factor that must be considered is sodium depletion In studies originally conducted by us in Toronto in Professor C H Best s laboratory we were able to show that dietary restriction of sodium in intact rats produced the same changes in JG cells as did adrenalectomy Excessive intake of salt caused the opposite change i e degranulation [4]

It is the purpose of this paper to discuss these three variables in regard to juxtaglomerular cells Because of the intimate relation of sodium adrenal cortex and hypertension it might be possible to find a common denominator

SODIUM INTAKE AND ADRENAL CORTEX

Following our initial experiments at Toronto involving dietary sodium we found that granulation of JG cells was related to width of zona glomerulosa of the adrenal cortex in rats fed either high normal or low sodium diets [5] Specifically increased granulation of JG cells was associated with widened zona glomerulosa Because of earlier work by Deane et al [6] we assumed that widening of zona glomerulosa represented hyperactivity and accordingly under these conditions JG cells became hypergranulated in the presence of excess mineralocorticoid activity Without the present knowledge concerning aldosterone however this interpretation was easily challenged

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Dunihue[7] was able to produce increased granulation of JG cells in rats but not in cats a discrepancy he believed due to a species difference Since feline JG cells responded well to adrenalectomy he again postulated that decreased mineralocorticoid was the stimulus and that adrenals of rats and cats might respond differently to sodium restriction Dunihue did not study histologic changes in the adrenals of his animals however and results from our recent experiments using rats dogs and cats are not compatible with his explanation

In weanling rats fed a sodium deficient diet an interval study (2 to 60 days) showed progressive hypergranulation and hyperplasia of JG cells a response similar to but of greater degree than that of adult rats Concomitant changes also progressive in nature included a fall in plasma sodium a widening of zona glomerulosa (to 8 times its normal width) and increased aldosterone secretion as determined by incubation of their adrenal glands[8 9] From these results it was clear that hypertrophy of zona glomerulosa correlated with increased aldosterone secretion confirming our previous conclusion that with sodium restriction JG cells were hypergranulated in the presence of excess mineralocorticoid activity Since adrenalectomy and dietary sodium deficiency affect JG cells in the same way the level of aldosterone cannot be the primary factor regulating granulation of JG cells The possibility still exists that sodium depletion might be this primary stimulus The following experiments deal with the question of species differences

Juxtaglomerular cells in the dog like those in man are sparsely granulated under normal conditions This species then would provide a good contrast to rats Littermate beagle puppies were used in order to provide adequate histologic controls and because previous experiments had revealed that sodium restriction produced more severe changes in young rats than in adult ones Although in reports concerning mature dogs peritoneal dialysis has been necessary to lower serum sodium in this experiment sodium depletion was produced by dietary means alone using a semi synthetic liquid diet Plasma sodium fell consistently during the first few weeks and thereafter remained low (about 125 mEq /l) Plasma electrolytes of control puppies fed the same diet to which adequate salt (1 3 per cent of dry weight) was added remained normal Juxtaglomerular cells and adrenal cortex were studied in step sections obtained by biopsy (3 weeks to 2 months) and at necropsy (up to 9 months) Width of zona glomerulosa was measured with an ocular micrometer and granulation of JG cells (JGI) determined by a counting method[5]

Without exception in the sodium depleted dogs zona glomerulosa became very wide Severity of this change increased with time giving a highly significant regression curve Zona glomerulosa in the same number of littermate controls remained constant The most striking feature was hyperplasia of glomerulosal cells which made adrenals of sodium deficient dogs readily distinguishable from normal (Figs 1 2) Race et al[10] reported hypertrophy of zona glomerulosa in dogs depleted of sodium by peritoneal dialysis but because this change was inconsistent the average increase in width of zona glomerulosa of sodium depleted dogs was not statistically significant Our positive results are probably explained by the advantage afforded by the young age of the dogs which made possible a sustained fall in plasma sodium by dietary restriction alone Like the zona glomerulosa, JG cells

Fig 1



Fig 2





Fig 3



Fig 4

Fig 1 Zona glomerulosa of the adrenal cortex from a control dog (Capsule at upper left beginning of zona fasciculata at lower right) Lipid is black Note how glomerulosal cells are lined up and arranged in convolutions Frozen section stained with Oil Red O and hematoxylin × 300

Fig 2 Zona glomerulosa of the adrenal cortex from a sodium deficient dog (4 months) photographed at the same magnification as Figure 1 (Capsule at the right) Because of extreme hypertrophy only a small portion of the width of zona glomerulosa could be included in the field at this magnification Note how the convolutions have become distorted compared to the normal and contain lipid only in the outer portions

became hyperplastic and hypergranulated (Fig 3) a constant finding of high statistical significance In control dogs JG granules remained sparse (Fig 4)

In another experiment, just completed at the present time sodium deficiency and adrenalectomy have been studied in kittens (2 to 4 months of age) Although cats are noted for refusal to eat special diets the same diet eaten by sodium deficient dogs was equally palatable to these kittens making force feeding and peritoneal dialysis unnecessary The adrenalectomized animals were treated with 2 5 to 5 mg cortisone twice daily and fed the control diet Juxtaglomerular cells of both sodium depleted and adrenalectomized kittens became hypergranulated and hyperplastic confirming results in rats and dogs Furthermore zona glomerulosa of the adrenal cortex was markedly hypertrophied and depleted of lipid in the sodium restricted group

From these experiments it can be concluded that a species difference does not explain the response of the rat to sodium deficiency In all three species studied dietary sodium restriction produced hyperactivity of both juxtaglomerular cells and zona glomerulosa of the adrenal cortex To determine whether these experimental results had a counterpart in human disease another study was undertaken [11] Renal tissue from 200 unselected consecutive autopsy cases was suitably fixed and stained for juxtaglomerular cells After counts had been done to determine degree of granulation information was obtained from hospital charts for possible correlation with clinical data Of the 200 cases only 23 had at least three electrolyte determinations during the last week of life the minimum number considered essential for the purpose of the study But these cases yielded the most interesting findings of this investigation Index of granulation of JG cells was inversely correlated with the level of serum sodium ($r = -0\ 61$ $p < 0\ 01$) Correlation with other data such as blood pressure potassium and NPN could not be demonstrated These results suggest that JG cells in man are functionally similar to those in experimental animals

HYPERTENSION AND RENIN

As mentioned above Goormaghtigh observed hyperplasia of JG cells in renal ischemia and implicated these cells in the etiology of hypertension His observations were confirmed by others among them Schloss [1] who studied hypertension in rats with constriction of one renal artery He found that while JG cells were hypertrophied in the ischemic kidney they disappeared in the contralateral kidney At Toronto we repeated this experiment in rats and also studied the effect of hypertension produced by unilateral ureteral ligation [13] In both cases JG cells were degranulated in the contralateral kidney and furthermore degree of granulation (JGI) in the unclamped kidney was inversely correlated with the level of blood pressure

Glomerulosal cells within the convolutions are hyperplastic Frozen sections stained with Oil Red O and hematoxylin × 300

Fig 3 Photomicrograph taken at the same magnification as Figure 4 of juxtaglomerular cells from a sodium-deficient dog (2 months) Note the striking hypergranulation and hyperplasia of JG cells compared to the normal Technical details as for Figure 4

Fig 4 Oil immersion photomicrograph of juxtaglomerular cells from a control dog (G = glomerulus MD = macula densa JG = granulated juxtaglomerular cells) Only a few granules can be seen in the juxtaglomerular cells Paraffin section Bowie stain × 1000

Unilateral nephrectomy did not alter granulation in the remaining kidney Tobian et al[14] also studied JG cells in hypertensive rats with one renal artery constricted They found that after weeks if the constricted kidney was removed or if a clamp was applied to the renal artery of the unclamped kidney granules were restored to normal in JG cells of the previously degranulated "untouched" kidney Dietary sodium restriction also caused partial restoration of granules In a later paper the same authors reported degranulation of JG cells in isolated rat kidneys subjected to high perfusion pressures for 1 to 4 hours[15]

From present evidence important experimental factors regulating granulation of JG cells can be summarized Renal ischemia low blood pressure and salt depletion (not only dietary restriction but also adrenalectomy) cause hyperactivity of JG cells while excessive sodium and high blood pressure depress JG cells Until recently we did not believe that all of the facts were compatible with Goormaghtigh's theory that JG cells might be the source of renin Dunihue[16] made an indirect comparison of conditions in which renin content of the kidney was known to change with conditions in which alterations in JG cells had been reported He concluded that evidence in support of Goormaghtigh's renin theory was indirect and circumstantial Later another indirect comparison of this type was brought to our attention by Gross[17] who tested pressor activity in crude saline extracts of rat kidney He and coworkers confirmed in the rat an increase in renal pressor active substances resulting from adrenalectomy and renal ischemia and found a decrease in pressor activity in the contralateral kidneys of rats with one renal artery clamped and in rats treated with DCA and salt[18] They did not study JG cells in their rats but it was obvious that these changes paralleled what was known to happen to JG cell granulation under similar conditions It had not been determined what happened to pressor activity (renin) in kidneys of sodium deficient rats

In preliminary experiments designed to extend these observations we have obtained some interesting results during the past few months[19] Using the method of Gross and Sulser[20] saline extracts were made from kidneys of sodium deficient and control rats after sections were taken for histologic study *The extracts were assayed in test rats that had been bilaterally* nephrectomized for one day Blood pressure was measured by direct cannulation of the femoral artery Pressor activity was expressed as maximum rise in blood pressure (mm Hg) produced by 0 1 cc of the original renal extract (1 cc of saline per gram of tissue) diluted to 1 50 with saline Pressor activity in extracts of kidneys from sodium deficient rats was much higher (48 mm Hg $p < 0\ 01$) than in extracts from control rats (24 mm Hg Fig 5) Degree of granulation of JG cells from these kidneys plotted against pressor activity (mm Hg) yielded a highly significant correlation coefficient ($r = 0\ 80$ 28 rats) Such a correlation provides more direct evidence for Goormaghtigh's renin theory and additional experiments of this type are in progress

Another preliminary experiment was carried out to determine what effect these extracts would have on JG cells when injected into normal rats for a period up to two weeks Five weanling rats (Group 1) were injected subcutaneously twice daily with 2 5 cc of a saline extract from a kidney of a sodium deficient dog with hypergranulated JG cells (0 1 cc equivalent to approximately 1 dog unit of renin) For control five comparable rats

(Group II) were injected with 2 5 cc of an extract with the same dilution (4 cc saline per gram of tissue) from a control dog with sparsely granulated JG cells Zona glomerulosa of rats in Group I was considerably wider (71 microns) than that of rats in the control group (53 microns $p < 0.05$) while degree of granulation of JG cells was less (JGI = 21) in Group I than in Group II (JGI = 42 $p < 0.02$) Assuming that degranulation of JG cells in these rats represents depression of secretory activity the results are what would be expected if the active extract provided an exogenous source of JG cell secretory product Secondly this extract caused widening of zona glomerulosa which may indicate increased aldosterone secretion Because

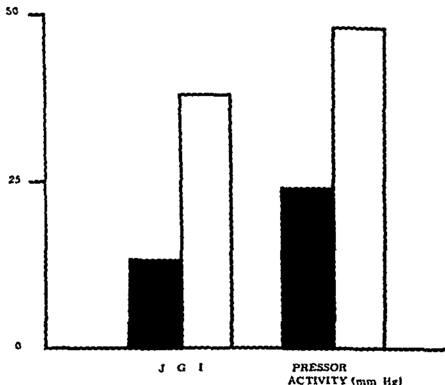


Fig 5 Degree of granulation of juxtaglomerular cells (JGI) and renal pressor activity in saline extracts of kidneys from the same animals Solid bars = Average of 14 control rats Open bars = Average of 14 sodium-deficient rats Differences between control and sodium deficient rats are highly significant ($p < 0.01$)

of the preliminary nature of these experiments the conclusions can only be tentative but they form the basis of our working hypothesis

SUMMARY AND CONCLUSIONS

Sodium deficiency in rats dogs and cats with resulting reduction in plasma sodium produces hyperactivity of zona glomerulosa (with increased aldosterone secretion) and hyperactivity of renal juxtaglomerular cells This relationship between JG cells and adrenal cortex can be interpreted in three possible ways (1) The effect of sodium depletion is coincidental with no functional relationship between the two This explanation is unlikely how

ever, because of statistical correlation between width of zona glomerulosa and granulation of JG cells (2) Sodium depletion stimulates zona glomerulosa which in turn causes hyperactivity of JG cells But this possibility must be ruled out because JG cells respond in adrenalectomized animals (3) Sodium depletion stimulates JG cells which in turn cause hyperactivity of zona glomerulosa *Although not proven this interpretation is compatible* with present evidence

If the third possibility is true that low sodium is a primary controlling factor then JG cells might be responsible for regulating aldosterone secretion by zona glomerulosa Though only preliminary in nature recent experiments indicate that Goormaghtigh s previous theory concerning elaboration of renin by JG cells might fit in with such a concept In sodium deficiency pressor activity of the kidney (renin) is increased in proportion to degree of granulation of JG cells and saline extracts of such kidneys cause widening of zona glomerulosa in intact rats

If sodium depletion stimulates renin production by JG cells then renin may in turn cause increased secretory activity of zona glomerulosa This pathway could implicate JG cells in the etiology of hypertension but in a *secondary role Such a concept is considered* compatible with the known facts and serves as a working hypothesis for further investigation

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The Effect of Increased Intrapulmonary, Intracardiac, and Intra-arterial Blood Pressure on Renal Sodium Excretion

M TOOR M DULFANO and J YAHINI with the technical assistance of F KATZ M Sc

Cardiopulmonary Laboratory Beilinson Hospital Petah Tikva Israel

The fact that sodium restriction lowers the blood pressure of some patients with systemic hypertension suggested that sodium is a pathogenetic factor in systemic hypertension A characteristic disturbance of the sodium metabolism in this disease is the hyperexcretion of sodium in the early phase of the disease This phenomenon is accentuated by infusion of hypertonic saline solution[1]

The purpose of this study was to search for possible alterations in sodium metabolism in patients with pulmonary hypertension due to mitral stenosis and in patients with hypertension localized in a restricted sector of the circulation namely right or left intraventricular hypertension due to pulmonic or aortic stenosis and to compare these alterations in sodium metabolism with those seen in systemic hypertension

MATERIAL AND CLASSIFICATION OF PATIENTS

Three groups of patients were investigated I mitral stenosis II pulmonic stenosis III aortic stenosis

I *Mitral Stenosis* 33 patients presenting clinical, electrocardiographic and roentgenologic evidence of predominant mitral

They were divided into groups as follows (Table 1)

Group A 6 patients with normal pulmonary artery pressure belonging to functional group II and early III according to the N Y Heart Association Classification [3]

Group B 17 patients of the same functional group II and early III but with high pulmonary artery pressure mean pressure range from 32 to 75 mm Hg

Group C 10 patients of functional group late III and IV with high pulmonary artery pressure mean pressure range from 30 to 62 mm Hg who showed evidence of failure at one time or another

The data of patients in group A are used as controls for groups B and C

II *Pulmonic Stenosis* 10 patients were investigated They were divided into two groups according to the right ventricular end diastolic pressure (Table 2)

A 7 patients whose right ventricular end diastolic pressure was not higher than 5 mm Hg

B 3 patients whose right ventricular end diastolic pressure was higher than 5 mm Hg

III *Aortic Stenosis* 13 patients were investigated They were divided into two groups according to the left ventricular end diastolic pressure (Table 3)

A 7 patients whose left ventricular end diastolic pressure was not higher than 10 mm Hg

B 6 patients whose left ventricular end diastolic pressure was above 10 mm Hg

Six normal individuals served as controls Their anamnesis was negative clinical and laboratory investigations were within normal limits (Table 4)

METHODS

All the patients and controls were kept on a low salt diet for the week preceding the studies All the investigations were carried out after a 12 hour fast period In mitral and pulmonic stenosis patients cardiac catheterization was performed according to the Cournand and Ranges technique [4] In aortic stenosis the left ventricular pressure was determined by the Brock direct percutaneous left ventricular puncture technique [5] Pressures were recorded by a Sanborn electromanometer Cardiac Index (C I) was calculated according to the Fick principle The blood gases were determined on a Van Slyke apparatus and the air gases on a Haldane apparatus Systemic pressure was recorded with an indwelling needle placed in the brachial artery Glomerular filtration rate (C_{IN}) was measured by inulin clearance and effective renal plasma flow (C_{PAH}) by sodium para aminohippurate clearance [6] All renal studies were made in the morning after a 12 hour fast period within 24 hours of cardiac catheterization [7] Blood and urine specimens were collected at the beginning of the experiments as controls A priming fast intravenous injection of 30 ml inulin and 4 ml PAH was given followed by a sustaining infusion of 25 ml inulin and 6 ml PAH in 300 ml 0 85 per cent saline regulated at a constant flow of 60 drops per minute After a half hour equilibration period was allowed clearances were performed at 10 minute intervals At the end of this stage the same amount of

TABLE 1 MITRAL STENOSIS

	B S A M	B P mm Hg	P A mm Hg	R A mm Hg	C I L/min / M	C p ml /m n		C ml /m		Na l d mFq /m n		r f N Lo d E c t d		U ry N E ret d mEq /m /M²			Uri ry Fl w ml /m n /M²		
						1		1		1		1		0	1		0	1	
C p A																			
N	6	6	6	6	6	6	5	6	5	6	5	6	5	6	6	5	6	6	5
M	148 5	7 83	15 0	9 0	2 80	577 63	519 96	86 5	100 6	11 9	1 09	1 14	1 46	0 031	0 09	0 123	0 87	3 99	1 05
S D	19 65	14 03	0 92	1 29	0 51	185 00	137 00	39 03	1 05	1 74	2 40	0 31	0 5	0 0 3	0 03	0 030	0 97	1 19	0 50
S E.	8 0	5 73	0 53	0 53	0 1	55 11	61 16	15 93	9 41	0 71	1 07	0 13	0 3	0 010	0 01	0 010	0 40	0 49	0 2
Cro p B																			
N	17	17	17	17	15	17	16	17	16	17	16	17	16	16	17	16	17	17	16
M	150 0	9 0	35 0	2 0	3 57	486 40	44 00	85 50	9 90	11 49	11 50	1 83	2 22	0 0 0	0 140	0 196	2 37	4 66	1 5
S D	16 9	15 34	12 43	1 39	1 10	1 5 00	01 0	0 57	19 76	2		0 59	1 15	0 04	0 04	0 150	1 92	1 4	1 3
S E	4 03	3	3 0	0 03	0 3	0 34	50 43	4 99	4 94	0 66	0 73	0 14	0 9	0 01	0 01	0 040	0 47	0 42	0 31
C p C																			
N	10	10	10	10	7	10	9	10	10	10	10	10	9	9	10	10	9	10	10
M	150 4	81 7	41 0	5 7	1 97	33 3	98 0	71 4	67 60	10 3	9 63	1 3	1 35	0 04	0 08	0 093	1 51	J5	0 73
S D	19 8	9 73	11	9	1 3 6	74 45	8 5	21 55	19 84	3 60	0	0 87	0 5	0 0 4	0 039	0 038	0 988	2 0	0 8
S E	6 10	3 05	3 54	0 88	0 42	23 56	7 4	6 8	6 28	1 14	0 85	0 8	0 28	0 008	0 012	0 012	0 3 9	0 0	0 09
C mp i n (p A B																			
N	3	3	3	23	1	3	21	3	1	3	21	3	1		3	1	3	3	1
D ff f M	1 50	1 0	0 0	1 0	0 77	91 3	7 96	0 75	17 7	3 05	0 59	0 69	0 6	0 039	0 050	0 073	1 500	0 670	0 200
S E f Diff	9 00	6 83	3 04	0 63	0 35	136 6	9 38	7 09	10 58	0 97	1 9	0 19	0 12	0 013	0 014	0 039	0 616	0 647	0 380
t	<1	<1	6 58	1 59		<1	<1	<1	1 67	3 14	<1	3 63	6 36	3	3 57	1 87	44	1 04	<1
C i i (r i A C																			
N	16	16	16	16	13	16	14	16	15	16	15	16	14	15	16	15	15	16	15
Diff f M	1 9	3 9	6 0	7	0 83	45 33	33 96	14 85	3 0	1 56	46	0 18	0 11	0 011	0 008	0 040	0 640	1 040	0 3 0
S E f D ff	10 07	6 50	3 56	1 03	0 54	59 91	67 15	8 49	11 6	1 34	1 37	0 30	0 37	0 01	1 00	1 00	0 518	0 952	0 41
t	<1	<1	7 30	2 62	1 54	4 09	3 48	1 5	84	1 17	1 79	<1	<1	≈1	<1	<1	1 24	1	1 33
C p i n G p B C																			
N	7	7	7	7		7	5	7	6	7	6	7	5	5	7	26	6	7	26
D ff f M	0 4	7	6 0	3 7	1 6	154 10	166 00	14 10	15 30	1 6	1 97	0 51	0 87	0 0 8	0 058	0 113	0 560	1 710	0 540
S E f Diff	7 34	4 83	4 65	0 946	05 6	127 0	57 41	8 45	99	1 3	1 12	0 31	0 40	0 01	0 015	0 039	05 3	0 814	0 319
t	<1	<1	1.9	3 01	8	1 1	2 2	1 67	1 91	<1	1 67	1 65	18	2 33	3 87	90	1 50	10	1 69

B S A B dy rf e re B P Dire t l tr rt i l blood pres d t m t P A M n p lm ary rt y p ess R A M n ight au ul pres re C I C rdi c i de C p n Me n ffecti re al plasm fl w C M n gl m ul r filtrati n t Na L d Filt red sod m l d.

TABLE 2 PULMONIC STENOSIS

Name	Sex	Age	BSA/ M²	B P mm Hg	R A mm Hg	R V mm Hg	P A mm Hg	C I L/min/ M²	ECG RVH	Strain
						Group A				
H R	M	14	1 62	100	4	85/ 24	1/4 16	4 5	+++	++
G F	M	10	1 41	90	3	70/5 20	13/7 10	4 8	+++	+
C M	M	13	1 30	95	2	75/3 17	15/8 10	3 8	±	−
P M	F	19	1 61	90	3	8 /5 20	15/5 10	2 2	++	+
M I	M	13	1 40	9	2	115/5 40	17 3 8	7 8	++	−
C M	M	44	1 85	1 0	2	66/4 25	15/10 13	3 6	+	−
I P	F	34	1 71	90	4	4 /6 14	2 /8 14	2 8	+	−
Number										
Range										
Mean										
						Group B				
M N	M	43	1 66	100	14	135/15 6	15/7 11	7	+++	+++
K S	F	0	1 67	90	5	130/10 60	13/6 10	1 9	++++	++++
L P	F	24	1 25	95	4	0/7 30	16/6 8		+++	++
Number										
Range										
Mean										

Legend as in Table 1 except for RV, Right ventricular pressure; PA, Pulmonary artery pressure.

inulin and PAH in 300 ml of 5 per cent sodium chloride solution was infused. Again a half hour of equilibration was allowed before proceeding with another three clearances.[6] Urine was collected through an indwelling multi-eyed catheter, the bladder rinsed with a measured amount of distilled water and air on completion of each emptying. Inulin was determined by the method of Roe et al.[8] and PAH by the method of Smith et al.[9] All chemical determinations were performed in duplicate. Values of inulin and PAH clearance were corrected to a body surface area of 1.73 M². The results recorded represent averages of three clearances. Plasma and urine Na were determined with the flame photometer.

TABLE 3 AORTIC STENOSIS

Name	Sex	Age	BSA/ M²	B P mm Hg	L V P mm Hg	ECG RVH	Strain
Group A							
A A	M	22	1 54	1 0 5	180 5 80	±	−
BH I	M	16	1 69	105/55	140 10 40	+	−
M Z	M	16	1 61	125/80	180/10 40	++	−
L A	M	40	1 67	180/80	190 10 85	++	+
F G	M	50	1 61	125/55	165/10 70	++	++
M L	M	48	1 74	80/50	30/10 60	++	++
V I	M	43	1 66	12 / 0	170/10 50	+	−
Number							
Range							
Mean							
Group B							
G M	M	19	04	80/35	166/15 100	+++	+++
N M	M	22	1 54	125/90	200/18 60	++	+
L L	M	6	2 00	110/54	200/18 40	+++	−
M A	M	17	1 36	120/60	190/ 0 55	++	−
M B	M	8	1 47	145/50	210/20 100	+++	+++
H B	M	50	1 88	100/65	270/40 100	++	++
Number							
Range							
Mean							

Legends in Table 1 except for LVP, Left ventricular pressure.

TABLE 2 PULMONIC STE\OSIS (Continued)

C H ml/m		C ml/m		Na Lo d mEq/m n		% f N Lo d F t d		Ur ry N F c ti mEq/m /M			U n ry Fl w c /m /M		
857 9	67	113 5	70 5	1 78	9 73	1 6	7 6	0 1 9	0 131	0 497	2 34	7	3 08
6 6 0	455 1	101 5	51 4	13 70	6 6	1 6	4 7	0 060	0 119	0 0	0 40	0 69	5 94
68 0	675 0	128 3	118 9	16 96	15 91	1 84	4 93	0 088	0 3	0 59	0 3	8 45	6 33
508 4	619 1	59 4	86 0	7 88	13 16	3 61	1 98	0 109	0 176	0 161	1 43	3 7	0 73
41 2	430 9	69 5	86 1	10 06	1 8	1 08	2 36	0 08	0 080	0 2	1 73	3 60	0 95
07 7	694 0	6 8	59 9	10 67	8 09	2 9	3	0 039	0 158	0 420	0 3	1 5	0 80
684 0	639 9	69 6	59 4	9 31	8 04	1 39	5 59	0 130	0 094	0 264	0 9	4 46	1.54
7	7	7	7	7	7	7	7	7		7	7	7	7
417 2	430 9	59 4	51 4	7 88	6 6	1 08	1 98	0 039	0 080	0 161	0 3	0 69	0 80
8 79	694 0	128 3	118 9	15 78	9 73	3 61	7 76	0 1 9	0 35	0 95	2 34	8 45	6 33
644 7	598 0	88 4	76 0	1 0	10 64	1 89	4 37	0 100	0 140	0 340	1 07	4 25	2 7
4 1.2	401 0	47 4	4 3	6 37	5 83	3 60	3 14	0 067	0 1 6	0 106	0 86	5 88	0 88
	554 1	67 2	71 6	9 54	9 74	1 59	2 18	0 044	0 081	0 123	0 49	5 01	0 96
399 0	328 3	99 4	95 8	13 9	13 80	2 04	23	0 098	0 6	0 56	1 71	9 44	1 58
2	3	3	3	3	3	3	3	3	3	3	3	3	3
393 0	3 8 3	47 4	4 3	6 37	5 83	1 59	2 18	0 044	0 081	0 106	0 49	5 01	0 88
4 1 2	554 1	93 4	9 8	13 9	13 80	3 60	3 14	0 098	0 6	0 256	1 71	9 44	1 58
409 6	4 7 8	71 3	69 9	8 94	9 9	2 41	5	0 0 0	0 148	0 16	1 0	6 78	1 14

RESULTS

Hemodynamics

In mitral stenosis patients (Table 1) the Cardiac Index (C I) rem uned within normal limits in groups A and B It w is lower than normal in group C The right auricul ir pressure w is within normal limits in groups A and B and slightly elevated in group C None of the patients in groups A and B had arterial uns ituration The arteriovenous difference was within normal limits in all

In pulmonic stenosis patients the C I was within normal limits in all

TABLE 3 AORTIC STE\OSIS (Continued)

C H ml/m		C ml/mi		N I d mEq/m n		% f Na L d E t d		U ry Na E et d mFq/m n /M			U ry Flow ml/m /M²		
6 6	360 7	91 4	49 6	13 8	7 30	3 65	9 03	0 190	0 331	0 474	0 87	4 13	3 35
547 6	90 1	83 6	80 7	12 46	1 43	3 73	4 41	0.2 1	0.275	0 3	8 63	6 56	1 40
65 0	401 7	115 8	71 3	16 67	9 01	2 6	3 15	0 053	0 119	0 177	0 5	0 54	0 68
4 2 9	385 6	88 4	68 6	11 89	9.51	3 3	4 89	0 141	0 37	0 275	0 6	2 87	2.57
472 7	3f1	87 7	5 7	11 86	7 33	1 23	4 74	0 05	0 091	0.215	0 99	4 77	2 96
378	425 4	57 6	64 6	8 1	9 56	1 18	6 45	0 025	0 055	0 354	0 59	0 59	5 9
464 9	648 7	97 0	107	13 60	15 73	2 72	3 26	0	0 3 8	0.299	1 37	3 5	3 5
7	7	7	7	7	7	7	7	7	7	7	7	7	7
378 2	360 7	57 6	49 6	8 12	7 33	1 18	3 15	0 053	0 055	0 177	0 25	0 54	0 68
765 0	790 1	115 8	107	16 67	15 73	3 73	9 03	0 23	0 331	0 4 4	8 63	4 77	5 9
531 1	481 9	88 8	77 8	12 55	10 14	2 6	5 1	0 129	0 208	0 30	1 90	3 14	2 79
639 6	544 9	8 6	83 9	10 39	10 8	1 29	1 70	0 074	0 01	0 135	0 30	6 30	0 5
578 8	512 3	104 0		14 3		0 65		0 037	0 050	0 14	0 26	5 50	0 71
545 7	6 7 4	9 1	96 3	1 76	13 89	3 06	3 52	0 151	0 0	0 246	2 01	6 80	1 68
5 3 4	453 5	87 5	101.5	12 07	14 21	1 8	1 86	0 0 0	0 114	0 194	0 15	1 19	1 47
	3 6 5	107 3	107 5	14 49	14 36	2 4	3 88	0 035	0 239	0 380	0 3	2 90	3 35
5f9 0	46 7	98 7	69 7	13 6	9 75	1 6	2 33	0 0f0	0 001	0 1 4	2 06	3 14	1 15
5	6	6	5	6	6	6	5	6	6	6	6	6	6
523 4	3 6 5	8 6	69 7	10 33	9 5	0 65	1 0	0 0 0	0 012	0 1 4	0 15	1 19	0 71
639 6	6 7 4	107 3	107 5	14 49	14 36	3 06	3 88	0 151	0 39	0 380	06	5 50	3 3
5 1 3	496	95 4	91 8	1 9	1 61	1 66	66	0 063	0 1 0	0.204	0 85	4 31	1 5

except for one patient in group B (K S) in whom it was low In pulmonic stenosis the systolic gradient was higher in group B than in group A In aortic stenosis the systolic gradient was also higher in group B than in group A (Tables 2 3)

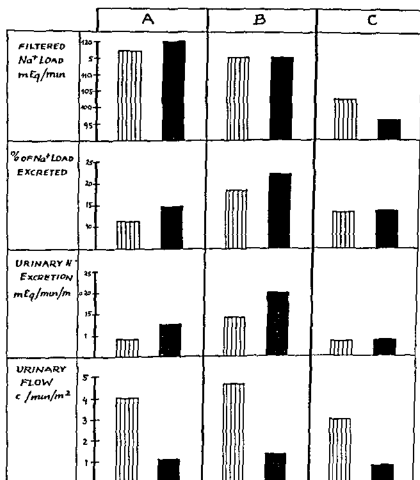


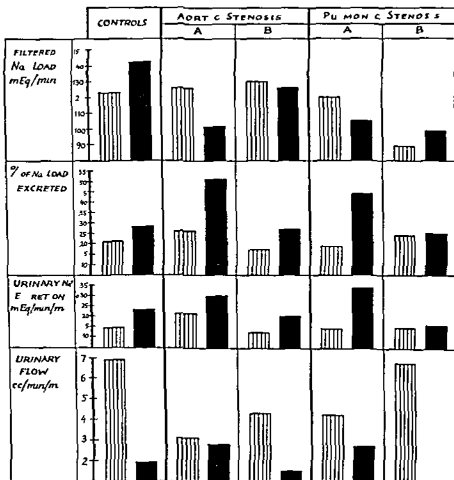
Fig 1 Renal dynamics in mitral stenosis

ECG In mitral stenosis patients no signs of right ventricular hypertrophy were found in group A patients whereas rather clear signs were found in group B and conspicuous ones in group C Both in pulmonic and aortic stenosis patients the respective signs of right and left ventricular hypertrophy and strain were more conspicuous in group B than in A

Renal Function

Renal Plasma Flow The mitral stenosis patients in group A had a mean renal plasma flow (C_{PAH}) within normal limits (Table 1)

Patients in group B had a diminished mean C_{PAH} It should be noted



A CLINICAL GROUP I II

B CLINICAL GROUP III IV

Following an intravenous infusion of 0 85% NaCl

Following an intravenous infusion of 5% NaCl

Fig 2 Renal dynamics in controls aortic stenosis pulmonic stenosis

that functionally they belong to the same group as patients in group A but are distinguished by their higher pulmonary artery pressure

Group C patients showed a definite decrease in mean C_{PAH}

The renal plasma flow is diminished in our patients even before any clinical sign of failure appears and is further decreased when failure supervenes This is in accordance with previous investigations [10]

In pulmonic stenosis patients the mean C_{PAH} in comparison with the controls in group A remained within normal limits but was low in group B (Table 2)

In the aortic stenosis patients the mean C_{PAH} was low both in groups A and B (Table 3)

After infusion of 5 per cent sodium chloride there is a reduction of C_{PAH} in group B of aortic stenosis patients

Glomerular Filtration Rate The mean glomerular filtration rate (C_{IN}) remained in the lower limits of normal in all the patients examined

Blood Sodium Blood sodium was within normal limits in all the patients examined

Sodium Excretion In mitral stenosis patients the filtered sodium load is slightly higher in group A than in group B Despite this the percentage of sodium load excreted is significantly higher in group B The urinary flow is also higher in group B than in group A (Fig 1) The filtered sodium load in pulmonic and aortic stenosis patients is practically the same as in the controls In spite of this the percentage of sodium load excreted after 5 per cent NaCl infusion in group A of both pulmonic and aortic stenosis is higher than in the controls Likewise the urinary flow following the 5 per cent NaCl infusion is higher in group A of both pulmonic and aortic stenosis than in the controls (Tables 2 3 4 Fig 2)

DISCUSSION

In selecting patients for mitral commissurotomy we noted that some patients in a relatively good functional state presented high pulmonary artery pressure values It therefore seemed of interest to study the pattern of sodium excretion after sodium load in pulmonary hypertension secondary to mitral stenosis and to compare this pattern with the sodium excretion in mitral stenosis patients of the same functional group but with normal pulmonary artery pressure

In comparing group A (pulmonary normotensive) with group B (pulmonary hypertensive) it can be seen that all hemodynamic values are nearly equal the only distinguishing feature being the elevated pulmonary artery pressure found in group B

Despite the lack of a significant difference in the filtered sodium load values between groups A and B the tubular rejection of sodium per minute expressed as per cent of Na Load Excreted is significantly higher in the group showing early pulmonary hypertension (B) This percentage decreases with the advent of heart failure (group C) [11]

Comparison of group A of pulmonic and aortic stenosis with the results obtained from 6 normal controls examined by the same technique showed that in patients with hypertension localized only in one of the ventricular cavities there was an increased tubular rejection of sodium in the early phase of the disease as there is in pulmonary and systemic hypertension

This pattern confirms our previous observation [1] We then studied 9 patients with isolated pulmonic stenosis and 8 patients with aortic stenosis A different technique was used namely the infusion of a 5 per cent NaCl solution and the pattern of sodium excretion was followed for 2½ hours [13] Seven normal individuals served as controls The pulmonic and aortic stenosis patients as compared to normals had a significantly higher sodium

TABLE 4 CONTROLS

Name	Sex	Age	BSA/M	B P	C_{PAH} ml/min		C_{IN} ml/min		Na Load mEq/min		% of Na Load Excreted		Urinary Na Excretion mEq/min/M			Urinary Flow cc/min/M²		
B H	F	37	1 58	90	693 _	523 0	98 1	87 5	13 64	12 31	2 70	3 26	0 165	0 235	0 257	3 66	7 84	1 75
S I	M	37	1 55	95	733 7	696 6	107 1	105 1	11 69	14 71	1 88	3 16	0 079	0 180	0 327	1 47	9 35	2 96
N I	M	29	1 61	95	573 0	587 0	76 8	82 2	10 56	11 09	1 29	2 59	0 004	0 083	0 178	0 42	3 34	1 04
H F	M	31	1 84	90	504 5	806 5	112 2	147 5	14 81	20 06	0 71	1 86	0 019	0 058	0 203	0 54	3 03	1 61
A S	M	28	1 88	100	640 0		77 7		10 49		3 90		0 112	0 218		0 85	10 37	2 84
S I	M	35	1 9_	95	728 8	727 9	72 4	95 4	9 85	12 87	1 85	2 81	0 043	0 095	0 188	5 42	7 29	1 34
N					6	5	6	5	6	5	6	5	6	6	5	6	6	6
Range					504 5	523 0	72 4	82 2	9 85	11 09	0 71	1 86	0 004	0 058	0 178	0 42	3 03	1 04
					733 7	806 5	112 2	147 5	14 89	20 06	3 90	3 46	0 165	0 235	0 327	5 42	10 37	2 96
Mean					649 8	668 2	90 7	103 5	12 34	14 22	2 06	2 50	0 070	0 145	0 231	2 06	6 87	1 92

Legend as in Table 1

excretion which was especially noticeable in the first 30 minutes after infusion (Fig 3)

Tests of sodium tolerance in experimental hypertension also revealed an increased urinary sodium excretion especially in the first half hour after the load[14]

The changing pattern of the sodium load excretion is assumed to be pathognomonic of systemic hypertension

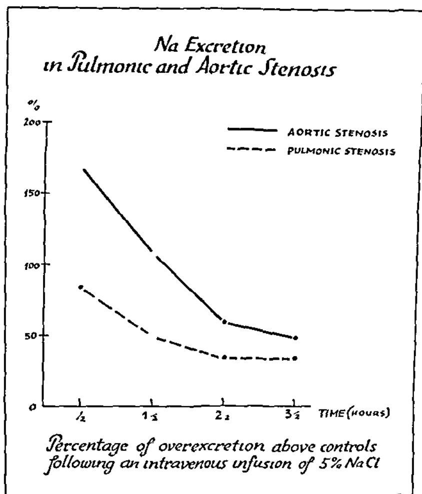


Fig 3

Our study which summarizes the results of 33 mitral 19 pulmonic and 21 aortic stenosis patients demonstrates that these patients in the early phase of their disease also display the phenomenon of sodium hyperexcretion even though they lack all signs of systemic hypertension It seems therefore that the changing pattern of sodium excretion from hyperexcretion in the early phase of the disease to hypoexcretion when heart failure supervenes is not pathognomonic of systemic hypertension only The common feature in all these pathophysiologic states is an increased intraventricular pressure It may therefore be suggested that increased intraventricular pressure alone

whether left sided due to essential systemic hypertension or aortic stenosis or right sided due to mitral or pulmonic stenosis alters the pattern of renal sodium excretion. This possibility is supported by the observations of O Connor[15] and Stamler et al [16] They found that occluding the carotid artery in normotensive dogs produced an immediate increase in blood pressure and there was concomitantly an increase in renal sodium excretion The increase in blood pressure implies the simultaneous increase in left intraventricular pressure

The mechanisms by which these changes in sodium excretions are produced when they do occur in patients with systemic hypertension also are not clear

Cottier and coworkers assume that the sodium clearance in systemic hypertensive individuals parallels arterial blood pressure up to a critical renal resistance ranging from 12 000 to 16 000 dynes/sec [5] beyond which it declines with increasing renal resistance [17] This cannot be a factor in our material the kidney being only the effector organ

Baldwin and coworkers proved that sodium hyperexcretion in hypertensives can be prevented by salt deprivation indicating that in hypertensives there is no tubular defect As sodium hyperexcretion could also be produced in normotensives by forced sodium intake they conclude that the exaggerated natriuresis in hypertensive patients has an extrarenal basis [18]

The distribution of total body sodium in systemic hypertension has been found to differ from that in normals [19] The possibility that this change affects the tubular rejection of sodium load through volume receptors remains to be proved

Multiple receptor effector arcs nervous and humoro-hormonal affect the renal sodium and water handling [9] In our study localized hypertension in one of the ventricles is enough to produce changes in urinary sodium excretion The changes in urinary sodium excretion of these patients may be triggered via baro- or stretch receptors in the ventricles and not only from the left auricle as described by Henry and Gauer [1]

Baroreceptors in both ventricles have been described by Paintal [2] However the presence of intraventricular baroreceptors or the anatomic exposure of a nervous receptor effector arc even if proved cannot alone explain the changing pattern of sodium excretion which is high in the first stages of the disease and decreases with the advent of heart failure despite the persistence of high intravascular and/or intraventricular pressure This effect on the kidney may probably be related to the functional status of the myocardium

In this study there is a correlation between the pattern of sodium excretion and the state of the myocardium as expressed by the end-diastolic pressure and the ECG findings The myocardium kidney connection however remains as yet unknown

SUMMARY

1 Hemodynamic and renal function studies were performed on 33 mitral 10 pulmonic and 13 aortic stenosis patients and the pattern of sodium excretion following sodium load was investigated

2 In clinical group II and early III the percentage of sodium excretion after sodium load was found to be higher in pulmonary hypertension and

in intraventricular hypertension whether right or left This is similar to the pattern of sodium excretion seen in systemic hypertension

3 The possible mechanisms of this phenomenon are discussed

ACKNOWLEDGMENTS

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Pathophysiology of the Nephron in Hypertension

WILLIAM DOCK

State University of New York Brooklyn

The blood vessels and the juxtaglomerular tissue of the afferent arterioles which show the most interesting and frequent changes in primary and secondary renal hypertension are not part of the nephron as usually defined and the changes in these renal structures have been discussed in the previous papers Changes in the glomerulus and tubules are evident only in those hypertensives whose rise in blood pressure follows renal inflammation or very marked destruction and compensatory hypertrophy of renal tissue In patients with benign hypertension who die of other causes before proteinuria is demonstrable our studies at Stanford University and Cornell prior to the war convinced us there was no decrease in perfusibility of the renal vasculature and no structural change in any part of the nephron including the macula densa the tubular component of the juxtaglomerular organ Also in rats made hypertensive by subtotal bilateral nephrectomy we could detect no change in the macula densa or in the rest of the nephron prior to the onset of hypertension and proteinuria Once proteinuria developed with marked glomerular hypertrophy there were the usual secondary changes in the tubules—vacuolization cast formation and storage of dyes such as Evans or trypan blue when these were bound to serum protein Our conclusion was that benign hypertension is not necessarily associated with any change in the function of the nephron or with its histologic structure More modern techniques such as electron microscopic study of the glomerulus undoubtedly will detect structural changes earlier and the type of study of tubules developed by Jean Oliver will detect tubular reabsorption of protein earlier than the methods we used However it seems a safe guess that in the early years of benign primary familial hypertension in man or in audiogenic hypertension in rats changes in the histology of the nephron are nil or minimal and will be found first in the vascular part of the juxtaglomerular organ and in the tubules only after changes occur in glomerular permeability to protein

It is worth noting that in shock one may detect mitoses in the macula densa both in man and in experimental animals This we noted first in material from British crush syndrome cases at the Army Institute of Pathology in 1943 but the studies of Dunihue[1] on rabbits are the best proof that changes in both macula densa and afferent arteriole can be evoked by shock It seems highly probable therefore that the juxtaglomerular organ evolved as part of the protection of the vertebrate from shock due to dehydration burns and lacerations hazards common to all species living under natural conditions Thus the changes which occur in heart failure and in benign hypertension can best be considered as responses to circulatory or nervous insults similar in effect although very different from those which influenced

evolution of the nervous hormonal and structural devices which protect the kidney and the whole organism against decreases in blood volume and cardiac output

One of the most remarkable facts about the kidney is its ability to survive complete cessation of blood flow for unusual periods of time while some glandular organs like the liver and the anterior pituitary are destroyed by relatively brief periods of inadequate blood flow It is probable that the main function of the juxtaglomerular organ and of renin is not to raise the general blood pressure but to protect the function of the kidney when pulse pressure in the kidney is reduced Schroeder and Steele[2] noted that when a Goldblatt clamp was gradually tightened the renal vascular bed became exquisitely sensitive to epinephrine and prolonged vasoconstriction followed doses given with the orifice narrowed to a critical point Pickering and Prinzmetal[3] noted that renin acted on the rabbits tubules much like cyanide so that a diuresis of fluid with the glucose and electrolyte content of plasma continued as long as blood volume was maintained and renin was administered Last year Huckabee in Boston observed that in all hypertensives the ratio of lactate to pyruvate was significantly increased in the urine as compared to normotensives[4] He concluded that all hypertensives must have sufficient tubular anoxia to cause a shift in metabolism from aerobic to anaerobic pathways Since in most benign and experimental renal hypertension renal blood flow is normal and rises normally on giving pyrogen and since renal vein blood from such hypertensive men and animals is red and has a high oxygen content the explanation offered by Huckabee must be accepted with reservation On the other hand if cyanide like paralysis of a tubular enzyme system can be effected by renin the observed shift in carbohydrate breakdown would occur In any event we may say that the only proved disturbance in the physiology of the nephron in all hypertensives is a shift of tubular metabolism from aerobic toward anaerobic type This may be due to increase in renin liberation

By paralyzing renal tubular metabolism renin liberated by the juxtaglomerular organ can protect the cells from prolonged anoxia By causing vasoconstriction of the efferent arteriole it can raise glomerular filtrate at any given level of renal blood flow and pulse pressure and this mechanism will be especially effective at elevated levels of circulating epinephrine such as can occur with painful injuries or alarming situations It should perhaps be recalled that the presence of a substance sensitizing the blood vessels of the rabbit to epinephrine was clearly demonstrated in pithed animals with renal hypertension as long ago as 1940[5] This substance apparently is not renin nor is the substance which changes the set of the vasoconstrictor center This makes it probable either that the juxtaglomerular organ in shock liberates two enzymes or that renin liberates the epinephrine sensitizing material from a substrate in the kidney

In summary even in benign familial hypertension the nephron has a disturbed metabolism with no histologic evidence of change from normal In other types of hypertension a similar disturbance in oxidative metabolism is present It may be due not to tissue anoxia but to an enzyme like renin which paralyzes a tubular oxidative enzyme system We still do not know the mechanism by which diminished vascular pulsation in the kidney causes the changes in the set of vasomotor center the secretion of aldosterone and the sensitivity of arterioles to epinephrine

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Discussion

WILLIAM DOCK *Moderator*

JOHN BEEM	H MITCHELL PERRY
QUENTIN DEMING	PAUL RHOADS
PHYLLIS HARTROFT	SHELDON SOMMERS
JOSEPH IMBRIGLIA	M TOOR
WILLIAM LIKOFF	ELLARD YOW
G M C MASSON	BENJAMIN ZWEIFACH

DR DOCK I will begin with a question from Dr Masson directed to Dr Sommers Ten years ago the hypothesis was presented that a vicious circle could be explained by secretion of renin and formation of angiotonin Renin itself has no pressor action but acts as a plasma protein splitting ferment to produce angiotensin which is a relatively smaller molecule with pressor properties Following the secretion of renin and the formation of angiotensin the glomerulosa of the adrenal is stimulated to produce a salt retaining corticosteroid Do your pathologic studies support or refute this hypothesis?

DR SOMMERS The adrenal changes we found in essential hypertension would indicate inactivity of the zona glomerulosa the cells being small and closely packed The inference is that aldosterone secretion was low normal or subnormal I could not infer any such vicious circle as was postulated There are other vicious circles which one could postulate from the pathologic material

DR DOCK Originally might there be some constriction of the afferent arteriole perhaps on a nervous basis followed by secondary changes in the glomerulosa and in the juxtaglomerular organ? Could this occur in the absence of any stimulation of the adrenal cortex?

DR SOMMERS Yes I think it could and perhaps does in the human being

DR. DOCK Dr Hartroft what have your studies of the adrenal cortex shown?

Dr Hartroft We investigated 200 necropsied cases and found enlargement of the zona glomerulosa to be correlated with hyponatremia but not with blood pressure When unilateral renal ischemia is produced in rats or rabbits there may be no relation between granules and the severity of hypertension In the contralateral untouched kidney degranulation occurs and is related to the severity of hypertension

Dr Dock In other words in the presence of hypertension the kidney unprotected by something on the artery leading to the glomerulosa shows degranulation

Dr Hartroft Yes that is right and Tobian has recently shown that in the isolated rat kidney high profusion pressures over a period of one to four hours produced the same degranulation

Dr Dock Dr Toor showed us that when we have full hearts we are glad to excrete sodium When the heart is working efficiently full of blood with a high intraventricular pressure then the kidney does not hold all the sodium avidly It drops an extra sodium load quickly When the heart fails even though the pressure in the heart is very high then the kidney does hold onto sodium very avidly Is that a correct statement of your findings?

Dr Toor It may be that this hyperexcretion of sodium is an early phase of decompensation It occurs not only in essential hypertension but in all other cases of elevated intraventricular pressure right or left Later on retention of sodium occurs

Dr Dock Members of the panel have reached different views based upon different experimental or clinical approaches Salt may be retained as a result of decreased flow into the glomeruli Shock or heart failure results in diminished blood flow to the tissues and retention of sodium It is evident that when cardiac output is adequate to meet the needs of the body the adrenal cortex is stimulated and aldosterone production is increased Dr Toor's experiments suggest certain questions If cardiac output is quite adequate for the needs of the body most of the time but the pressure in one or both ventricles is high do the adrenal cortex and the sodium retaining mechanism of the kidney idle? This situation really is just the opposite of shock and the least possible stimulus for sodium retention is present The salt retaining mechanism is stimulated in the presence of decreased cardiac filling or decreased blood flow If the heart is adequately or greatly filled with blood because of the hypertensive state and normal blood flow to all the tissues is maintained presumably you would have the ideal state for releasing sodium

Dr Sommers The various organs of the body probably react to immediate stress situations on an individual basis The heart may not recognize the total plasma volume and the needs of the whole organism It responds to local stimuli in local reflex manners It is not surprising to observe a response of neurologic type from the heart which you might describe as inappropriate to the needs of the kidney or the brain

Dr Dock That is just the point we want to clarify The impulses coming from the heart for retaining sodium would be maximal when the heart is inadequately filled during the development of shock The impulses from the

rest of the body are minimal when there is an optimal blood flow to all the organs Thereupon the body would have the least need to retain sodium and the stimulus to the adrenal cortex for producing aldosterone would be minimal

Let us return to the important problem of pyelonephritis Fifteen per cent of your hypertensive patients were found to have chronic pyelonephritis at surgery I imagine many had not been suspected of having pyelonephritis prior thereto This then is a very important cause of hypertension Even more important is so called primary hypertension in which most of us believe that the Goldblatt phenomenon is not operating in any organic sense at least initially Do you agree that organic Goldblatt lesions do not initiate primary hypertension?

DR SOMMERS We have not found any Concerning pyelonephritis a small renal biopsy is not an accurate way of estimating the incidence of pyelonephritis in the entire hypertensive population

DR DOCK The demonstration of a 15 per cent incidence of pyelonephritis by small renal biopsy in a group of hypertensives from which you have excluded the previously known pyelonephritics emphasizes the magnitude of this problem However the slide of Dr Homer Smith's that I showed you illustrates the important point that primary hypertension is not initiated by organic renal disease but by renal vasoconstriction due to impulses from the vasoconstrictor center which acts with unusual vigor on the afferent arterioles of the kidney This constitutes a functional type of Goldblatt kidney in which the glomerular flow is reduced and at the same time presumably the juxtaglomerular tissue is stimulated In most patients this does not produce immediate stimulation of the adrenal cortex as indicated by the fact that most hypertensive patients excrete a sodium load rather quickly In the early stages of primary hypertension we have no evidence that the glomerulosa of the adrenal is producing excessive aldosterone However there [illegible] some evidence that hypertensive patients when given a low salt diet [illegible] adequately conserve sodium during the first week than normal people [illegible] normal person when changing from an average diet of 8 or 10 [illegible] sodium chloride a day to a diet with only 200 mg of sodium require[illegible] haps a week before he stops losing weight and begins to conserve [illegible] chloride by reducing excretion through his kidneys and sweat [illegible] In hypertensive patients this adjustment occurs more rapidly [illegible] adaptation to sodium restriction in the hypertensive individual [illegible] in spite of an absence of sodium retention when salt loading is [illegible] normal diet such as Dr Toor described Primary hypertension [illegible] acterized by evidence of hyperaldosteronism or excessive [illegible] activity even though we would expect the juxtaglomerular [illegible] stimulated as the afferent arterioles are somewhat constricted [illegible] filtra[illegible] tion fraction is relatively high as shown by Dr Homer S[illegible] others

Dr Masson asked me about the endocrine kidney The [illegible] kidney that does not atrophy when a renal artery is marke[illegible] the epithelial tissue adjacent to the glomerular vascular [illegible] is the macula densa Presumably this epithelial tissue is [illegible] portance in the pathogenesis of hypertension

Recently a lay report emphasized the sensitivity of the arterioles to epinephrine in hypertension Dr Zweifach you were the first one to work experimentally in this field and to have shown that this is due to something in the plasma The recent lay report announced that hypertension was now under control and that there was an absence of something that caused hypertension you thought that there was a presence of something with a pressor action Do you want to come back to this problem of how renin or something in the kidney sensitizes the arterioles?

DR ZWEIFACH We have demonstrated in the blood of experimental animals and clinical hypertensive subjects the presence of a substance which causes small blood vessel hyper reactivity in laboratory animals That is the basis of the concept We have no direct visual evidence of comparable hyper reactivity in the small blood vessels of man although the conjunctival vessels may be hyper reactive under certain conditions You asked if vasoconstriction is due to a positive pressor or sensitizing agent or to interference with the destruction of these amines A positive agent can still interfere with the destruction of O methyl transferase or monamine oxidase thereby allowing pressor amines to remain active at that site for a longer period of time I know of no evidence demonstrating an inhibitor of O methyl transferase or any other enzyme acting upon the amine

The substance Dr Ephram Shore and our group worked with many years ago does not produce vasoconstriction of isolated strips of arteries such as the aortic strip or profused small blood vessel It was pressor only in intact animals We thought it involved some neurogenic components but perhaps it involves some inactivation system rather than directly changing the sensitivity of vessels

DR DOCK One of the curious findings in experimental renal hypertension and in human hypertension is the sensitivity to smaller doses of norepinephrine or epinephrine However there is no evidence that epinephrine or norepinephrine is an important factor in producing the hypertension

DR ZWEIFACH You are invoking the neurogenic pathways in the initiation of hypertension I presume from your questions to Dr Sommers Presumably this involves some neurohumoral mediation

DR. DOCK When you administer an adrenolytic agent such as Regitine to most primary hypertensive patients thereby blocking the action of epinephrine and norepinephrine *the blood pressure does not fall* Even though one can demonstrate something in the plasma of hypertensive patients which sensitizes blood vessel response to epinephrine this may not be the basis of the hypertension

DR ZWEIFACH The juxtaglomerular apparatus contains granules which appear and disappear and we indicate functional activity on this basis We talk about various stress situations resulting in degranulation of the apparatus Suppose this releases renin? I think we could just as easily talk about mast cells which degranulate easily in any stress situation to which you refer Is it not possible for some amine which is known to degranulate mast cells also to degranulate juxtaglomerular cells?

Juxtaglomerular cells are located strategically in reference to the afferent arterioles We know that the local climate can be influenced by the release

of substances by cells of this character Is it not likely that these cells as a wide variety of cells such as mast cells in various areas of the body are releasing other amines known to greatly alter the reactivity of smooth muscle? Indeed mast cells release esterases and nonspecific enzymatic products Must we assume that juxtaglomerular cells are releasing something peculiar to the kidney?

DR HARTROFT I cannot answer that question Your suggestion has not been ruled out

DR DOCK It is quite possible that these cells release something which acts on the efferent arteriole to raise the filtration fraction in that particular nephron very quickly Perhaps this substance acts on the local macula densa and influences the metabolism of the tubular cells of that nephron The fact that the juxtaglomerular apparatus is present in every renal unit makes it seem quite likely that it is there to act mainly on each renal unit separately

DR HARTROFT The proximity of the macula densa is a very intriguing consideration and in electron micrographs this proximity is even more striking It appears on preliminary study that there may be channels between juxtaglomerular cells and the macula densa Anatomically and otherwise, it seems that the macula densa is just as important as the juxtaglomerular organ in the total reaction but the signal probably comes from the juxtaglomerular organ on the afferent arteriole Assuming the normal stimulus to this tissue to be a low pulse pressure in the renal artery or renal arterioles as is known to produce hypertension then the theory would fit rather neatly

DR DOCK An interesting patient with hypertension resulting from disease of one-half of one kidney was observed at the Veterans Administration Hospital in Brooklyn The man developed hypertension retinal changes and disabling headache in a period of six weeks He was cured by the removal of the right kidney only the upper half of which was abnormal and histologically resembled the endocrine kidney described by Selye Hemorrhage had occurred in an atherosclerotic plaque in the main renal artery branch supplying the upper half of the kidney Thus only one quarter of the total renal tissue received inadequate pulsation and severe hypertension resulted It is important to realize that three quarters of your total renal tissue may not protect you from a poor pulsation in one-quarter of your total renal tissue

DR SOMMERS Dr Russel Street demonstrated an identical case at the New England Society of Pathologists The gross picture was very striking with half a kidney nephrosclerotic and the other half which had a partial vascular obstruction remained completely undamaged

May I ask Dr Hartroft a couple of questions? Does the staining quality of the granules in the juxtaglomerular cells suggest anything about their composition? Secondly when the apparatus degranulates in which direction does it do so—toward the vascular lumen or toward the tubular lumen?

DR HARTROFT Histologic or cytologic observations have not defined the direction in which secretion takes place Our current studies with electron microscopy may help answer this question McManus found the granules to

be PAS positive they are not feulgen positive The Boure stain is not specific enough to draw any conclusion There appears to be a lipoid complex probably a lipoprotein in these granules

Dr Dock Purified renin is only protein without any lipid is it not?

Dr Zweifach Nobody has completely purified renin as an enzyme

Dr Dock Material with a very low lipid content has renin activity This adds to the mystery of what is coming from the granular cells Nevertheless they are degranulated mainly when they are not functioning It is the juxtaglomerular organ of the kidney without a Goldblatt clamp that is degranulated

Dr Hartroft We interpret this as depression of activity because hypergranulation occurring in the opposite situation is associated with hyperplasia and you must use both criteria to determine whether secretory activity is increased or decreased We believe that hyperplasia with hypergranulation definitely indicates increased activity and degranulation indicates decreased activity

Dr Dock More renin may be extracted from the kidney with the most granules?

Dr Hartroft *Yes It is related to the granule content of JG cells*

Dr Dock This is one of the instances in which secretory tissue not only increases its secretion but also its cells contain large amounts of the secretory product In other tissues a different secretory activity results in the cell depleting itself whereupon it appears empty at a time when it is extruding large amounts of hormones We do not know what the juxtaglomerular organ is producing We know that renin has been extracted but everything in the entire cortex is extracted because the glomerulosa is not separated from the macula densa in the process Consequently we do not know whether the granules are renin or whether the adjacent macula densa is producing renin and the juxtaglomerular organ is producing some other substance The latter might stimulate the macula densa or act directly on the efferent arteriole to produce focal renal vasoconstriction thereby increasing the filtration fraction Dr Homer Smith first demonstrated the effect of postural hypotension fainting and emotional hypertension upon filtration fraction Studies *this last year have shown the kidney in any type of hypertension to have a* metabolism approaching that which *you would expect with renal anoxia* This is very important evidence that all sorts of profound changes are occurring not merely in stimuli to other blood vessels which would produce the renin type of hypertension but changes in the kidney itself

Dr Toor in your studies any degree of heart failure invariably stimulated the mechanism for sodium retention is that correct?

Dr Toor Yes In every case we examined slight heart failure was associated with sodium hypoexcretion

Dr Dock In many of these of course there was no arterial hypertension at the same time In pulmonic stenosis with congestive failure the arterial blood pressure can be on the low side of normal

Dr Toor It should be emphasized that this alteration in sodium excretion which I have described occurred while the systemic pressure was normal

Dr Dock In mitral stenosis there is a tendency to have hypertension according to several investigators Dr Samuel Levine in reviewing data collected at the Peter Bent Brigham Hospital in Boston during the last 50 years found middle aged women with mitral stenosis to have an increased incidence of hypertension However I think this is the only group of patients with heart trouble in whom hypertension is demonstrable statistically The so-called Stalling Hoeks group has been emphasized for years and many normotensive patients become hypertensive while developing congestive failure Is that correct?

Dr Toor I analyzed the data on 500 patients with mitral stenosis and congestive failure at our hospital The incidence of systemic hypertension in these cases was very low In all cases of intraventricular hypertension right or left systemic arterial pressure was normal There was no Stalling Hoek group

Dr Dock The British particularly Dr Pickering believe that mitral stenosis is unassisted with systemic hypertension You agree with the British that severe heart failure with marked sodium retention may occur without any rise in blood pressure?

Dr Toor I would say so

Dr Dock This is a little awkward for your thesis Dr Hartroft because heart failure is certainly accompanied by a reduction of renal blood flow and a diminution of arterial pulsation Marked sodium retention occurs without the development of hypertension This is a problem that may be studied in experimental animals In Dr Hamilton s laboratory experimental mitral stenosis has been produced in dogs resulting in severe salt retention and adrenocortical hyperactivity in the absence of hypertension This may be a method for dissociating the effects of the juxtaglomerular organ from hyper trophy of the zona glomerulosa of the adrenal

Dr Hartroft I should emphasize that we are not suggesting that JG cells cause hypertension but that they may be involved in the pathogenesis of hypertension by action on the zona glomerulosa This does not imply that every time juxtaglomerular cells appear hyperactive hypertension must be present

Dr. Dock Must hyperactivity of the zona glomerulosa always be a result of stimulation coming from the juxtaglomerular organ? I think this is where the theory is likely to break down The zona glomerulosa probably can be stimulated by several mechanisms The kidney may be one source of stimu lation and Dr Hartroft s observations point to the juxtaglomerular organ All of us realize that primary or secondary hyperaldosteronism may occur without any hypertension We must not consider hyperaldosteronism and hypertension as being inseparable We might generalize that each of the mechanisms which have to do with hypertension or salt retention may be activated and perpetuated by several different stimuli A given mechanism is not a simple machine with a single line of current going through a single

wire There are many wiring systems available both for production and for the maintenance of these disturbances

DR ZWEIFACH From the pathologic viewpoint Dr Sommers and Dr Imbriglia have shown the initially evident lesion in hypertension to be an arteriolar change followed by a series of pathologic manifestations of the disease Do pathologic observations give you any idea of how the disease is perpetuated? Are the structural changes you have described part and parcel of the perpetuation mechanism and are they causally related or are they secondary?

DR SOMMERS It should be emphasized that the predominant lesion is always tubular degeneration and this alters the tubular transport of sodium and other substances I agree that the initial arteriolar change appears to be a neurogenic spasm Later when an organic arteriolar lesion is present I believe a renal mechanism is initiated which sustains the elevation of dias tolic pressure

DR DOCK I think Dr Zweifach s point was that once the renal lesion has progressed histologically to a certain extent does this in itself maintain the hypertension?

DR SOMMERS The mathematical relationship between average diastolic pressure and grade of renal arteriolar sclerosis is thought to indicate such an effect at least beyond grade I

DR DOCK This whole problem of renal hypertension is extremely com plicated When Dr Goldblatt presented evidence that a renal pressor sub stance caused hypertension it was generally thought for a number of years that hypertensive disease was the result of a simple renal pressor substance that worked like epinephrine or Pitressin or something of that sort It turns out that the problem is more complex After renal hypertension has been present for a few weeks the blood pressure elevation is maintained by altered vasomotor center activity and sympathetic nervous impulses Even in chronic glomerulonephritis and pyelonephritis splanchnicectomy or sym patholytic drugs may reduce blood pressure to virtually normotensive levels It seems that even in renal hypertension something is acting on the vasomotor center Renin injected into a susceptible animal causes an eleva tion of blood pressure upon frequent repetition of the injection the hyper tensive response becomes progressively less and finally the blood pressure fails to rise This is a state of tachyphylaxis A rabbit with renal hypertension of the Goldblatt type also has a further rise in blood pressure upon the administration of renin It also becomes tachyphylactic but when it is com pletely tachyphylactic to renin its blood pressure is just as high as it was before you gave it any renin In other words it has a hypertension that is not renin hypertension and is still present when renin no longer has any pressor effect Thus renal hypertension involves mechanisms that so far as we can tell at the moment have nothing to do with the original action of renin in liberating angiotensin from plasma protein This indicates the com plexity of this problem on the one hand and on the other is the fact that we can now treat all types of hypertension except pheochromocytoma more or less successfully by sympathectomy or by drugs which block sympathetic action High sympathetic nervous tone is an important perpetuating mech

anism in both renal and primary hypertension This hypertension is not due to a humoral substance which sensitizes the vasculature to epinephrine or one which acts directly like the pressor substance angiotensin For this reason the management of hypertension has become much more effective

We now realize that blockade of sympathetic nervous impulses results in effective therapy not only in primary hypertension but also when a renal element is superadded Particularly in accelerated hypertension in which there is major renal vascular damage sympathetic blocking drugs or sympathectomy is very useful in prolonging life

It appears that Dr Goormaghtigh s original concept is correct the purpose of the juxtaglomerular organ is to protect the kidney from shock raise the blood pressure and increase the cardiac output This applies to all varieties of shock Unfortunately this machinery works very well even in the absence of shock when essential hypertension or pyelonephritis with secondary hypertension occurs

Pyelonephritis as a Cause and Complication of Hypertension

ELLARD M YOW and TORU SAKUMA

Baylor University College of Medicine

A quarter of a century has passed since Longcope[7] first described the close association of these two conditions pyelonephritis and arterial hypertension. During the next decade there appeared additional important contributions[2,3,5,6] including the memorable work by Weiss and Parker[4] Since these pathologic and clinical descriptions of the relationship between pyelonephritis and infection of the kidney were published little specific information concerning this association has been added One of the principal reasons for this paucity in information is that hypertension rarely occurs as a part of the acute pyelonephritis but usually only after repeated acute attacks have occurred or the disease has become chronic This means that if the natural history of pyelonephritis with its late manifestations is to be understood there must be some means of following closely the pathology and clinical signs and symptoms of the disease over a period of many years Those changes due to active infection and those due to the residual injurious effect on the renal vessels glomeruli and tubules which progress after the infection has been controlled must be differentiated from similar changes that might occur as a part of other intercurrent diseases or for that matter as a part of the aging process itself

The understanding of the relationship between hypertension and pyelonephritis has been further limited by difficulties in making the precise diagnosis of pyelonephritis in its chronic stage Until recently even the histo

logic study of the kidney when these two conditions existed was made after the patient had died from one of the complications of either renal failure or hypertension and the microscopic changes in the kidney were so advanced that they were often indistinguishable from those of other advanced renal diseases The lack of active means of terminating the infectious process of pyelonephritis prior to the antibiotic era seemed to discourage general interest in these common but potentially serious ailments Even after antimicrobial agents were developed capable of controlling almost all of the bacterial diseases the management of pyelonephritis has remained a frequent problem because of its relative refractoriness to chemotherapy in many instances and because of the difficulty in determining when healing has taken place

ETIOLOGIC ROLE OF PYELONEPHRITIS

The fact that elevated arterial blood pressure occurs so commonly in patients without infections of the kidney has led some investigators to *question the causal relationship between pyelonephritis and hypertension* However the frequent occurrence of both diseases in the same subject during life (as high as 23 per cent of all hypertensive patients have renal infections according to Grieble et al[11]) and the frequent finding of active or healed pyelonephritis at autopsy in patients who had hypertension strongly suggests that pyelonephritis is at least one of the causes of hypertension

While it is true that acute pyelonephritis rarely produces hypertension unless it is superimposed on chronic or healed pyelonephritis or other renal vascular disease arteriolar sclerosis may develop in a relatively short period of time[6] This is most frequently seen in severe interstitial pyelonephritis or pyelonephritis associated with ureteral obstruction such as often occurs during pregnancy or in association with renal stones or prostatic obstruction One would expect hypertension to be a frequent finding in the necrotizing papillitis of diabetes but so few patients have survived this diagnosis that its natural history in patients not dying of the disease is not known

Under certain circumstances the effect of pyelonephritis seems to be that of greatly aggravating hypertension due to benign nephrosclerosis The rapid course of malignant hypertension terminating in uremia in a few months was thought to be due to the superimposition of infection in 15 to 20 per cent of the series of patients studied by Weiss and Parker[4] The evidence of active and severe renal infections has been so consistently found in patients dying of malignant nephrosclerosis in the experience of Saphir and Taylor[8] as to lead these authors to believe that infection is the factor converting benign essential hypertension with its concomitant benign nephrosclerosis to the rapidly progressing malignant phase

The effect of pyelonephritis on the structure and function of the kidney varies a great deal just as infection in the lung produces a great variety of changes in lung structure and pulmonary function These variations depend on many factors including the characteristics of the organisms producing the infection the type and degree of preexisting vascular disease of the kidney the presence or absence of structural abnormalities of the excretory system of the kidney the extent of the penetration of the infection into the kidney parenchyma the duration and severity of the activity of the infec

tious process and the ability of the host to withstand infection generally Decreased renal function of some degree is almost always associated with pyelonephritis of any degree of severity but hypertension may or may not follow Classically the atrophic kidney of longstanding infection is most consistently associated with hypertension The specific change in the kidney playing the determining role as to whether the inflammatory reactions produce hypertension or not is the degree of arteriolar sclerosis produced

DIAGNOSTIC ASPECTS

Diagnosis of acute pyelonephritis creates slight if any difficulty clinically Pyuria, local tenderness around kidneys and systemic manifestations point to the renal infection Nevertheless the chronic disease with quite an insidious onset and few or no subjective symptoms is really a matter of great concern Those patients with this type of infection possess only minimal signs of renal infection and progressive renal insufficiency may be the predominant manifestation They often lack any remarkable number of pus cells in the urine Albuminuria of low grade may be the only abnormality detected in the urine Emphasis must however be placed on the management of this kind of case since it is quite likely that the control of infection may be able to prevent the progress of renal inflammatory change which eventually produces hypertension In this respect reliable quantitative urine cultures pale cell preparations of the sediment and possibly needle biopsy of the kidney should be employed as often as feasible in addition to the complete urologic examination in individuals suspected of having anatomic disorders Particularly as stressed by Schreiner[9] arterial hypertension beginning in the age groups below 25 and above 50 without history of vascular or renal disease should receive serious consideration for the possibility of masked underlying pyelonephritis

There are certain clinical features which may aid in distinguishing hypertension of pyelonephritic origin from hypertension primarily on a vascular basis In pyelonephritic hypertension despite severity of the elevation of arterial blood pressure and advanced findings in the retina generalized atherosclerosis cerebral vascular accidents coronary disease and thrombosis are not as likely to be prominent On the other hand, central nervous system symptoms are often encountered The patients complain of headache dizziness tinnitus anorexia etc Increased cerebrospinal fluid pressure up to 400 mm H_2O has been reported Renal tuberculosis hydronephrosis and cystitis are by themselves not responsible for hypertension but not infrequently superimposed pyelonephritis brings about an elevation of arterial pressure in these conditions Also congenital cystic and aplastic or hypoplastic kidneys are liable to the infection and may be associated with hypertension The common occurrence of degenerative disease of the cardiovascular renal systems with infections of the urinary tract often makes it quite difficult to determine the relative role of each in the production of the hypertension

Recently Woods[10] reported the results of an experiment which might be interpreted as a supportive ground for the concept that hypertension predisposes to pyelonephritis In this study rats were made hypertensive by the use of desoxycorticosterone acetate injection and oral administration of saline solution following unilateral nephrectomy An *E coli* suspension was

then inoculated into the veins of those rats Twenty three of 33 hypertensives developed pyelonephritis in contrast to only 2 out of 33 controls with positive results

Clinically it appears to be probable that hypertension or renal vascular change *secondary to the elevated* blood pressure might render one more susceptible to this type of infection Attacks of pyelonephritis tend to recur Also experimentally various forms of injuries to the kidney are likely to induce the infection These seem to warrant further careful evaluation of the reverse and mutual relationships between hypertension and pyelo *nephritis*

SUMMARY

1 The frequent occurrence of hypertension and infection of the kidney strongly suggests that pyelonephritis is one of the causes of elevated arterial blood pressure

2 Acute pyelonephritis rarely produces hypertension unless it is super imposed on chronic pyelonephritis or other preexisting renal disease

3 The renal vascular changes associated with pyelonephritis play the determining role in the production of hypertension

4 Pathologic data indicate that acute renal infection may convert benign nephrosclerosis with mild hypertension to a rapidly progressing malignant phase

5 More precise methods of recognizing chronic and asymptomatic pyelonephritis must be utilized to clarify the role of pyelonephritis in the production of hypertension and to evaluate methods of controlling the infection These include in addition to the commonly used methods quantitative urine cultures and renal biopsies

6 There is suggestive experimental evidence in animals not only that pyelonephritis produces hypertension but that hypertension predisposes to renal infection

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The Incidence and Clinical Importance of Pyelonephritis in Patients with Hypertension*

PAUL S RHOADS

Northwestern University School of Medicine

INCIDENCE

Although Longcope[1] and others had previously pointed out the frequent association of hypertension and pyelonephritis the present interest in an etiologic relationship stems chiefly from the classic studies of Weiss and Parker in 1939 These workers found that in the focal areas of inflammation occurring in pyelonephritis there was acute arteritis arteriolitis and endarteritis of the productive and later the necrotizing type the latter changes being seen only in the chronic and healed stages of the disease They drew a relation between the severity and the diffuseness of the changes and the degree of hypertension—pointing out the similarity to the severe obliterative vascular lesions found in malignant nephrosclerosis but emphasizing that in the latter the lesions are more generalized throughout the body In the series of Weiss and Parker 15 to 20 per cent of patients with hypertension in the malignant phase had pyelonephritis In studying their autopsy material they found that among 38 persons with pyelonephritis in the chronic or healed stage 68 per cent had *some* degree of hypertension

Longcope and Winkenwerder[3] had found 5 of 9 patients who had been suffering from pyelonephritis for many years to have hypertension Limited autopsy studies also had indicated that hyaline sclerosis of arterioles in the kidneys pancreas adrenals and intestines was present in the patients having pyelonephritis associated with hypertension while these changes were not seen when the patients were normotensive Because these lesions were not extensive Longcope was not sure of an etiologic relationship

Maher and Wosika[4] in a study of 600 patients with hypertensive vascular disease found that 101 of them had urologic abnormalities of some type over half of which seemed to be associated with pyelonephritis While pointing out that the majority of patients with pyelonephritis probably do not develop hypertension Braasch and Jacobson found that the incidence of hypertension is higher in patients of all ages with the malady than in those who do not have urinary tract infections In the patients in the third fourth and fifth decades of life those with pyelonephritis had hypertension almost twice as frequently as in controls of the same age Hayman[6] states that hypertension occurs in only about one fourth of all cases of pyelonephritis but in those cases with demonstrable impairment of renal function it is present in about 50 per cent

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Kinney and Mallory[7] in 1000 autopsies at Boston City Hospital found healed pyelitis in nearly 14 per cent of all persons. The lesions were sometimes of minor degree and in life many of the patients had had few or no clinical manifestations referred to the kidneys. However, the number of these patients who eventually developed renal failure or significant hypertension exceeded the number with subacute or chronic glomerulonephritis.

Our own studies[8] would support the contention that microscopic evidence of pyelonephritis is present in more than 20 per cent of all patients autopsied, but we do not have satisfactory figures on the incidence of hypertension in the group studied. Fishberg[9] states that if both the acute and chronic forms of pyelonephritis are considered it is doubtless the most frequent of all kidney disease. He thinks "a high proportion" of all patients with the affection develop hypertension and that the *majority* of those progressing to contracted kidneys do so.

Clinicopathologic correlations such as those of Weiss and Parker constitute strong presumptive evidence for a causative role on the part of chronic pyelonephritis in the development of hypertension. However, much *more definite proof is afforded by the cases of unilateral pyelonephritis in* which removal of the diseased kidney resulted in a significant and prolonged reduction in blood pressure.

The first such report was by Butler[10] in 1937. By 1952 Tanquist[11] had collected 81 cases in which unilateral pyelonephritis associated with hypertension had been treated by removal of the diseased kidney. Fifty-seven per cent had experienced some drop in blood pressure after the operation. Pickering and Heptinstall[12] described 11 cases in which one kidney had been removed for suspected unilateral renal disease in hypertensive patients. It was found that 4 of these had *bilateral* pyelonephritis and 1 had tuberculosis of the kidney. None of these were benefited by nephrectomy. Of the remaining 6 with unilateral pyelonephritis, 5 had a significant fall in pressure maintained for many months during which they were under observation. The others had experienced no real change in their condition. From his experience with these and 3 more such cases studied subsequently, Pickering[13] concludes that improvement can be expected in about one half of such cases but the drop in blood pressure is not quite to the expected norm. Other mechanisms have come into play to maintain the blood pressure. It is of importance that 7 of his 9 cases were symptomless as far as the urinary tract was concerned. The lesion was discovered on routine intravenous pyelography on persons studied simply because they had extremely high blood pressures. Many more reports have appeared since those cited, the favorable results being about as predicted by Pickering.

Obviously an exact estimate both of the number of patients who suffer from pyelonephritis and of the proportion of those in which it is a factor in contributing to the development of hypertensive vascular disease is impossible. It must be clear from the figures cited, however, that the recognition of urinary tract infections is of utmost importance in the management of patients with high blood pressure of *any* degree or duration. If these infections are *found early* and controlled, some of the irreversible vascular changes which chronic pyelonephritis causes may be prevented. If they are found late, at least the patients may be made more comfortable. If unilateral pyelonephritis, even advanced enough largely to destroy one kidney's

function is discovered in persons whose other kidney is unaffected remarkable cures may sometimes be effected by removal of the diseased organ

DIAGNOSIS OF PYELONEPHRITIS

The picture of acute pyelonephritis with a sudden rise in temperature often accompanied by chills pain in the lumbar region and flank painful and frequent urination, and gross or microscopic hematuria and pyuria is so characteristic that it can scarcely escape recognition However the chronic cases offer more difficulty

In the quiescent and chronic phases the diagnosis is much more difficult Jackson[14] and his associates state that of the nephritis found at autopsy without recognized antecedent genitourinary disease chronic pyelonephritis is present in at least 50 per cent of the cases Often when the patient presents vague symptoms of chronic fatigue weakness anemia inability to gain weight and occasional bouts of unexplained fever the examiner with a high degree of suspicion may be able to elicit a story of a few mild attacks of "kidney trouble in early childhood or during pregnancy Sometimes there is the complaint of infrequent periods of mild dysuria frequency or urinary infection sometimes no story of urinary disturbance past or present

Laboratory Diagnosis Of the objective findings which should excite suspicion the presence of pus cells in the urinary sediment is the most constant In *chronic* pyelonephritis proven by unilateral nephrectomy Jackson and his associates found an excess of leukocytes in the urine in 78 per cent—more than 10 to the high power field were found in the urinary sediment of 58 per cent Our own experience is that even in routine specimens from female patients passed with no special cleansing of the genitalia the presence of more than six or eight leukocytes to the high power field more often than not is associated with a positive urine culture

Proteinuria is present in more than half the cases of longstanding urinary infections both in the healed and active phase All authors agree however that quantitatively it is apt to be less in amount than when the proteinuria is due to advanced glomerulonephritis or other renal lesions Waxy and granular casts may or may not be present Red blood cells usually indicate the presence of an *acute* infection or of some chronic lesion such as renal lithiasis tumor or ulceration with which the urinary infection is associated Since chronic pyelonephritis is probably the most common cause of uremia[9] any patient with persistent azotemia should be a suspect

Often the obvious presence of an obstructing lesion such as a neurogenic bladder large cystocele known urethral stricture or symptomatic hypertrophied prostate leads to the almost certain conclusion that pyelonephritis must be present Because it is present four times as commonly in diabetics who come to autopsy as in other persons it should always be strongly suspected in all diabetics whose hyperglycemia suddenly gets out of control without other manifest reasons

The first step in definitive diagnosis is identification of the causative microorganisms With few exceptions satisfactory cultures of the urine can be made from male patients by washing the glans penis and urethral meatus thoroughly with soap and water having the patient pass a few milliliters of urine and then collecting a mid stream specimen in a sterile container Except when there is a large cystocele or atony of the bladder

such mid stream specimens are satisfactory for females also provided the nurses will take sufficient care in the preparation and instruction of the patient Such cultures have much more value if they are quantitative A simple technique which we use routinely in our clinical work is to inoculate two Petri dishes containing an appropriate solid medium one with exactly 0.1 ml of the mixed uncentrifuged urine and the other with 0.1 ml of a 1 100 dilution of the urine—using an appropriate broth as the diluent By counting all of the colonies growing on each plate a fairly accurate estimate of the number of bacteria per milliliter of urine can be obtained If the count is under 10 000 colonies per milliliter it is very unlikely that the positive culture represents anything more than contamination with the bacteria of the 2 cm of the urethra which lie nearest the orifice A study now in progress[15] supports this contention Other authors[14, 16] have taken a bacterial count of 100 000 as admissible for the conclusion of contamination

TABLE 1 CAUSATIVE MICROORGANISMS IN 1174 CASES OF URINARY TRACT INFECTIONS

	NO OF CASES	PER CENT OF TOTAL
E coli	450	46.39
Streptococcus faecalis	192	19.79
Pseudomonas aeruginosa	98	10.10
Staphylococcus albus and aureus	61	6.28
B proteus	57	5.87
Aerobacter aerogenes	48	4.94
M tuberculosis	25	2.67
G tetragenus	13	1.34
Kl pneumoniae	12	1.23
Hemolytic streptococcus	4	0.41
N catarrhalis	4	0.41
B subtilis	2	0.20
Alcaligenes faecalis	1	0.10
Pneumococcus	1	0.10

Multiple microorganisms—204 cases (17.37%) Of these the combination of E coli & Enterococcus occurred in 76 cases (6.47%)

rather than true infection The exact figure must of course be an arbitrary one For practical purposes a Gram stain of the urinary sediment will serve to differentiate significantly infected urine from urine contaminated by catheterization In our experience at least it is uncommon to find more than an occasional colony in cultures when the Gram stain of the centrifuged urinary sediment has failed to reveal bacteria In many instances when mid stream specimens have revealed a growth of bacteria more abundant than the arbitrary limit but contamination is suspected regular catheterized specimens must of course be cultured both to settle this issue and to determine with certainty which bacteria are the actual invaders The distribution of bacteria in 1174 urine cultures made by us is listed in Table 1 It will be noted that in 17 per cent of the cases two or more microorganisms were present in the original cultures a fact that is of importance in the choice of antibacterial therapy When cultures were made subsequent to a single round of treatment the original microorganism cultured had been replaced by another in 25 per cent of instances (Table 2)

Culture of "clean" or catheterized urine is emphasized as the first step in the recognition of chronic pyelonephritis because effective antibacterial therapy depends on knowledge of the etiologic agent Also the decision as to whether further diagnostic or therapeutic procedures by the urologist are in order often depends upon whether or not active infection is present In our experience about 7 per cent of patients with pyuria had no bacterial growth and about 15 per cent with positive cultures had no pyuria Hence pyuria cannot be taken as the sole criterion of the presence of chronic pyelonephritis By the same token negative cultures cannot invariably be taken as evidence that the infection is inactive In rare instances a patient with high fever signs of acute toxicity and even bacteremia may be encountered in whom a severe infection is present in the renal parenchyma (embolic abscess) or renal pelvis but in whom no bacteria are present in bladder urine because of a blocked ureter In such cases of course vigorous antibacterial treatment is required in spite of a sterile urine culture These patients may be greatly improved by the time pus and bacteria may be found in the urine

TABLE 2 ANALYSIS OF RESULTS IN URINARY TRACT INFECTIONS RESULTS OF RECULTURES AFTER A SINGLE COURSE OF ANTIBACTERIAL THERAPY

	NEGATIVE	POSITIVE FOR ORIGINAL ORGANISM	CHANGE FROM ORIGINAL ORGANISM	TOTAL CASES	INFECTION PERMANENTLY CONTROLLED	
Infections associated with obstructive *lesions of the upper* urinary tract	24 (22 9%)	46 (43 8%)	35 (33 3%)	105	8 (7 6%)	10 8%
Infections associated with obstructive lesions of the *lower* urinary tract	63 (28 9%)	92 (42 2%)	63 (28 9%)	218	27 (12 4%)	
Infections with *no* obstructive lesion found	74 (48 5%)	54 (35 2%)	25 (16 3%)	153	51 (33 3%)	
Totals	161 (33 8%)	192 (40 3%)	123 (25 8%)	476	86 (18 1%)	

Equal in importance to determining the causative bacteria is discovery of the degree of renal impairment and of any obstructive lesions that can be corrected All patients with severe hypertension should have a blood chemistry study including urea clearance determination of the level of non protein nitrogen creatinine and the blood proteins and the ability of the kidney to concentrate urine If no severe degree of azotemia is present all patients even remotely suspected of having pyelonephritis should have intravenous pyelograms If stones ureteral strictures or abnormalities of the renal pelves are revealed by the latter the need for cystoscopy is clear However it has been estimated by Nesbit and Conger[17] that 22 6 per cent of patients with definite pyelonephritis have normal pyelograms and that the

changes are minimal in another 54 7 per cent Hence it appears that if the history urinary or blood chemistry findings are suggestive of recurrent or longstanding infectious kidney disease cystoscopic investigation is indicated

TREATMENT

While a defeatist attitude should not be taken it must be apparent to urologists and internists alike that most cases of longstanding pyelonephritis cannot be cured However the progress of the process may be arrested in many cases if with the aid of the urologist the defect responsible for the infection in the first place is searched out and dealt with along with vigorous and prolonged antibacterial therapy

TABLE 3 LOCATION OF OBSTRUCTING LESIONS OR PROBABLE SOURCE OF INFECTION IN INFECTIONS OF THE URINARY TRACT IN 548 CASES

Urinary infection with no roentgen or cystoscopic evidence of obstruction —134 (24 45%)

Lesions obstructing outflow of urine—414 (75 54%)

UPPER URINARY TRACT LESIONS		LOWER URINARY TRACT LESIONS	
Renal or ureteral calculus	58	Urethral stricture or urethritis (including congenital stricture)	81
Hydronephrosis—obstruction at ureteropelvic junction	27	Benign prostatic hypertrophy	63
Nephroptosis with obstruction	16	Carcinoma or papilloma of the urinary bladder	34
Tumor of kidney or ureter	15	Cystourethrocele	32
Tuberculous pyelonephritis with secondary infection	13	Spinal cord lesions and indwelling catheter	25
Ureteral stricture	11	Acute prostatitis	9
Double kidney and ureter	10	Interstitial cystitis and elusive ulcer	8
Polycystic disease of kidneys	1	Acute or chronic vaginitis	5
Pyelitis of pregnancy	1	Fistula between bladder and vagina or bowel	4
		Calculi in urinary bladder	2
	152 (36 7%)		262 (63 28%)

Table 3 summarizes the experience of Dr V J O'Conor chief of the urologic service at Chicago Wesley Memorial Hospital and the author in the location of lesions associated with acute and chronic pyelonephritis in 548 cases It will be seen that in 24 45 per cent of urinary infections there has been no evidence of an obstructive lesion and that roughly two thirds of such lesions are in the bladder or urethra and one third in the ureter kidney pelvis or kidney parenchyma The most frequent obstructions and the ones most amenable to treatment are cystourethrocele in women prostatic hypertrophy in men and urethral stricture in both sexes The rather dismal results depicted in Table 2 were compiled at a time when quantitative cultures were not being done so that any bacterial growth whatever in recultures made 48 hours or more after cessation of antibacterial treatment were taken as evidence of continuing infection By methods used at present the results might have appeared slightly more favorable Even so the fact remains that when these patients were observed over long

periods only elimination of obstructing lesions along with antibiotic or chemotherapy proved effective in controlling the process

Unilateral functionless or nearly functionless kidneys usually are discovered by intravenous pyelography Confirmatory diagnostic aids include retrograde pyelograms plain films of the abdomen aortography renal biopsy and cystoscopy with differential renal function tests performed on each kidney A recent addition to this group is the Diodrast renogram in which the dye is labeled with I^{131} [18] Scintillation counters determine the rate of accumulation and rate of clearance of the dye in each kidney and thus give useful information on the function of each

Since pyelitis is present in perhaps one half of the cases of unilateral poorly functioning kidneys a search for its presence is of importance

SUMMARY

The incidence of pyelonephritis in patients with hypertension has not been computed with certainty but probably exceeds that in the general population and is probably above 20 per cent

Since it very frequently is associated with malignant hypertension and is known to produce intimal thickening of arteries and arterioles such as is seen in other types of nephritis associated with hypertension the assumption that it is an important cause of hypertension seems warranted This concept is supported by the fact that removal of one kidney in which there is pyelonephritis with extensive arteriolar changes of this type from hypertensive persons whose other kidney is relatively uninvolved results in significant improvement in the hypertension

Steps in the diagnosis of pyelonephritis are described and the point emphasized that for permanent improvement in these patients the obstructive lesions which produced the pyelitis must be recognized and dealt with

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Discussion

WILLIAM DOCK *Moderator*

JOHN BEEM	PAUL RHOADS
QUENTIN DEMING	HENRY SCHROEDER
PHYLLIS HARTROFT	SHELDON SOMMERS
JOSEPH IMBRIGLIA	M TOOR
WILLIAM LIKOFF	ELLARD YOW
G M C MASSON	BENJAMIN ZWEIFACH
H MITCHELL PERRY	

DR DOCK Pyelonephritis is of such very great importance that it should be discussed now Dr Sommers in those patients in whose tubules you saw signs of degeneration which apparently was the earliest lesion found how *often was proteinuria associated with the renal tubular degeneration?*

DR SOMMERS We have not correlated that clinically I suspect in at least half

DR DOCK As glomeruli begin to leak, the tubules promptly reveal changes *resulting from excessive reabsorption of amino acid and of protein itself* from glomerular filtrate This is often described as a degenerative lesion I think that is true in some cases

DR SOMMERS We distinguished hyaline droplet nephrosis and it was only found in 0 25 per cent of our entire series of cases

DR DOCK Proteinuria?

DR SOMMERS Hyaline droplet nephrosis is the ultimate tubular lesion accompanying proteinuria I do not know however that you can equate hyaline droplet nephrosis in proteinuria

DR. DOCK This occurs with very severe proteinuria in the early stages there may be less striking tubular alterations As soon as protein begins to get into glomerular filtrate or reabsorption of glucose fails pyelonephritis

may develop much more readily than it would otherwise Dr Rhoads you meant to indicate that hypertension predisposes in some such way to pyelonephritis even in experimental studies such as those done by you and by Dr Yow s group There is a two way action wherein proteinuria or glycosuria predisposes to progressive pyelonephritis and most cases of pyelonephritis subacute or chronic predispose to hypertension However one of the mysteries is the patient with progressive chronic pyelonephritis leading to uremia without ever developing hypertension Dr Rhoads do you have any idea what percentage of fatal pyelonephritis runs its course without hypertension?

Dr. Rhoads No I do not All authors point out that it occurs only in the contracted scarred kidney In the acute phase of pyelonephritis there may be a large intensely inflamed kidney and uremia without the development of hypertension presumably because arteriolar or arterial changes have not yet occurred

Dr Dock However in glomerulonephritis there are no changes in the arteries and yet in the acute phase hypertension and headache almost always occur with this purely glomerular lesion Renal hypertension can occur in acute glomerulitis but is usually absent in the early stages of acute interstitial pyelonephritis Do other panel members know how often chronic progressive pyelonephritis with uremia occurs without any hypertension?

Dr Deming No one can satisfactorily answer that question For one reason it is extremely difficult to distinguish pyelonephritis The clinician in my experience is frequently unable to make this diagnosis as judged by subsequent pathologic study Although the pathologist has a much better chance of being correct than the clinician microscopists often disagree in the interpretation of the same sections Therefore I think it is impossible to answer your question at the present time

Dr Dock You mean that one pathologist would diagnose only a terminal pyelonephritis and another would think that there was chronic pyelonephritis?

Dr Deming No I mean that subjecting one slide to the microscopes of three excellent pathologists we get the diagnosis of chronic pyelonephritis from one chronic glomerulonephritis from another and uncertainty from the third

Dr Schroeder I support Dr Deming s contention In my experience patients with all the criteria for a diagnosis of chronic pyelonephritis with abnormal pyelograms may develop the malignant stage years later die and the necropsy diagnosis be either chronic glomerulonephritis or arteriolar nephrosclerosis with necrotizing arteriolitis I have also seen patients who clinically had definite chronic glomerulonephritis yet at necropsy had chronic pyelonephritis One classic case was studied from the first attack of acute nephritis until death in the late twenties This case presented to students year after year a classic example of acute nephritis progressing to chronic glomerulonephritis She did not have it at necropsy

Will you make a distinction for us between hypertension with and without azotemia with pyelonephritis? I think mechanisms of azotemic hypertension may differ from those of nonazotemic hypertension We know sub

stances in the blood may change and produce a moderate hypertension with uremia

DR DOCK Yes of course uremia may work two ways A patient with chronic hypertension may develop uremia and the hypertension may become less severe as he begins to lose sodium and retain potassium because of his glomerulonephritis Another patient may become more markedly hypertensive as uremia develops The pathologist cannot easily tell the clinician when a pyelonephritis started and when it ended Scarring can take place in a few weeks or certainly in a few months Consequently it is very difficult for the pathologist confronted with the end product to tell where the original glomerulonephritis ended and the pyelonephritis became superimposed This can be done only when clinicians study the urinary sediment somewhat more carefully than to indicate the number of cells in a high power field The question is how the high power field was prepared For instance ten cells may represent the sediment in one half or one-tenth of a cc after centrifuging down 15 cc When there is a large piece of sediment in the centrifuge tube and it is allowed to remain in considerable water before making the suspension only two cells per high power field may be seen when actually the patient has pyuria and the urine is grossly turbid Thus the standard method we all use for describing urinary sediment is about as unquantitative as anything could be particularly when we do not look at the round cells to see if they are polymorphs or not We practically never make smears of them and most people do not examine them carefully under high power Therefore most people who look at urinary sediment have no idea how much suppuration is occurring and this adds to the pathologist's difficulty in deciding when the glomerulonephritis was engrafted or when the malignant hypertension was superadded It is very difficult to reconstruct the disease process by a pathologic study of the kidney and knowledge of only the last six months of the patient's clinical course The Addis system of studying the urine sediment whereby a sudden increase in the number of polymorphs in the urine is readily detected, is of considerable assistance in correlating the clinical course with subsequent pathologic sections

Dr Yow and Dr Rhoads wanted to emphasize I think that improvements in antibiotic therapy should shorten the course of pyelonephritis much more effectively than has been possible in the past Dr Rhoads how successful is modern antibiotic therapy in creating constantly sterile urine in patients with nonobstructive types of chronic pyelonephritis?

DR. RHOADS We are not as successful as we would like to be Our methods are more precise we have more antibiotics antibacterial agents and better sensitivity tests Our treatment is more precise We have come to the conclusion certainly that we must treat these people for longer periods of time at least two weeks Nevertheless continued observation indicates that they are not cured unless their obstructive lesions are corrected In the 10 per cent that had complete relief of clinical symptoms each patient had correction of an obstruction such as urethral strictures or prostate disease Antibacterial agents give excellent and quick symptomatic relief but relief of obstruction is essential

DR DOCK Dr Yow what can be done for the ones without the obstructive lesions?

Dr. Yow I am more optimistic than Dr Rhoads At least you have given me a more favorable group to work with those patients without obstruction To cure pyelonephritis the disease must be considered serious when it first appears to be present It must be recognized early and treated intensively on the basis of a carefully planned program utilizing active carefully selected agents Thereby quite a number of them can be cured or at least the urine cultures become negative We have examined serial renal biopsies on a few patients before during and after treatment and at least some of them appear to be actually cured as indicated by the disappearance of the characteristic microscopic inflammatory process Such results are possible particularly in patients with acute interstitial pyelonephritis in which the specific etiologic organism is isolated the number of organisms determined quantitatively and specific therapy instituted promptly The disease can be cured at least in some of those people

Dr Schroeder My experience supports Dr Rhoads and Dr Yow About twenty years ago Dr Steele and I found that approximately 40 per cent of severe hypertensive patients under the age of 40 had abnormal intravenous pyelograms We also examined 50 young men referred by the draft board because of labile slightly elevated blood pressure Thirty seven (or 74 per cent) of these had abnormal pyelograms or their urine when cultured contained organisms at that time considered to produce the sclerosing low grade noninflammatory type of pyelonephritis that we commonly encounter It was possible to repeatedly examine about a dozen of those people and they had continuous colony counts in the same range every day twice a week or three times a week for months I urge that young males with slightly elevated blood pressure be examined urologically

Dr Dock Dr Schroeder most of those lesions were above the ureteral orifices in a region where corrective procedures are difficult were they not? Urologic intervention is most efficacious for obstructive lesions at the trigon or external thereto is it not Dr Rhoads?

Dr Rhoads Yes that is right

Dr Dock Lesions above the ureteral orifice are less amenable to surgical cure and we formerly thought they caused no back pressure or difficulty

Dr Schroeder They cause stasis which of course is the locus for infection

Dr Dock Well many of these were bifid ureters and things like that

Dr Schroeder We had bifid ureters many uretero pelvic junction obstructions and an occasional large hydronephrosis

Dr Dock Those are all amenable to therapy Most of those lesions at the lower end of the pelvis are correctable Consequently in your experience young men with hypertension have a high incidence of remedial obstructive renal disease or an unsuspected chronic pyelonephritis Is that the essence of your observation?

Dr Schroeder Young men with slightly elevated blood pressure or indeed people under 40 years of age

theoretical approach to this problem of salt and hypertension The amount of salt lost by a hypertensive compared with a normotensive individual while on a low salt diet is perhaps 40 mg a day The amount of sodium chloride in a normal diet is approximately 10 gm a day This 40 mg difference between the two does not seem very great compared with the average salt intake

Dr Schroeder Forty mg is a large amount in the sense that in 10 days it becomes 400 and in 100 days it becomes 4 gm and that constitutes a salt deficit in the whole body

Dr Dock The difference in salt loss between hypertensive and normotensive individuals has been demonstrated during periods of severe sodium restriction I think that under other circumstances balance studies would not confirm any sodium retention in the normotensive as compared with the hypertensive subject Analysis of the arteries of hypertensive individuals reveals excess sodium It must have come from somewhere

Dr Rhoads Dr Dock I would like to return to the subject of pyelonephritis for just a minute One question has troubled me greatly In pyelonephritis hypertension is not troublesome unless there is severe renal vascular damage proliferation of media and intima Why does pyelonephritis cause this type of vascular damage in the kidney when chronic infection in the lung or elsewhere does not?

Dr Dock Most of us have seen arteriosclerosis in the arteries next to tubercles in the meninges and in the coronary arteries with tuberculous pericarditis I suspect this is a fairly common reaction of arteries to adjacent inflammation and that it is not peculiar to the kidney Any other views on this? Dr Sommers?

Dr Sommers There are many problems in pyelonephritis to which there are no answers However if the lung is an analogy then you do see arteriolarsclerosis and arteriosclerosis in the lung much more often than is recognized clinically I agree with Dr Rhoads that unless arteriolarsclerosis *accompanies pyelonephritis no hypertension results A person is predestined* to get hypertension if the proper situation develops including infection in the kidneys

Dr Rhoads Then you think that it does not occur more often in the kidney than elsewhere?

Dr Sommers My understanding of the previous discussion was that hypertension leads to these arteriolar changes and therefore you would expect a good correlation between the clinical presence of hypertension and the pathologic presence of the arteriolar changes If I understand Dr Rhoads he is suggesting that the pyelonephritis must first produce the arteriolar change and then there would be hypertension However since the arteriolar changes occur in hypertension of almost any etiology I should expect them to occur in the older more conventional order

Dr Dock I think Dr Rhoads conceded that when hypertension developed in pyelonephritis the arterioles in the kidney would show the same changes as those in the adrenals *and the pancreas and elsewhere It was the*

early arterial lesions that appear in the kidney before they are present anywhere else in pyelonephritis that he was interested in

DR SOMMERS Dr Dock he didn t say that the lesions were there before they were present anywhere else In order to know that you would have to biopsy the rest of the body

DR DOCK Well some of these people have died long before biopsies were done and there was autopsy evidence on this long before that

DR RHOADS When Longcope first considered this question he was afraid to relate arteriolar changes in the pyelonephritis kidney to hypertension because he didn t see comparable changes in the arterioles of the gut lung or elsewhere such as he saw in malignant hypertension of other etiology I think almost everybody will agree that quite often the changes of arteriolarsclerosis occurring secondary to hypertension are more nearly confined to the kidney The studies of Kincaid Smith and Longcope would suggest that in hypertension associated with pyelonephritis there is considerably more of this arteriolar change in the kidney than in other tissues as compared to malignant hypertension of other etiology

DR SOMMERS Dr Rhoads I did not mean to argue that the kidney was not unusually vulnerable to arteriolar changes My only question is why one should assume that the arteriolar change precedes the hypertension rather than the other way around The available data indicate that when hypertension is present the arteriolar changes are present which comes first we do not know When pyelonephritis is present without hypertension it does not produce the arteriolar change When hypertension is present without pyelonephritis it does produce the arteriolar change or at least is associated with it Therefore to assume that pyelonephritis leads to arteriolar change and the latter causes hypertension is the less likely explanation

DR DOCK Is a diffuse renal lesion without specific vascular changes the cause of hypertension in pyelonephritis rather than the vascular lesions in the kidney?

DR SOMMERS You re pushing me Dr Dock I do not know what is the cause of hypertension in pyelonephritis I would guess that it is an anatomic accident That is the reason hypertension occurs in some and not in other cases of pyelonephritis is that the Goldblatt like phenomenon takes place in some part of the kidney in some cases and not in others It probably has nothing to do with the type of organism or the particular appearance of the scar tissue The location of the vascular lesion is of prime import

DR SCHROEDER I think Dr Sommers stated the crux of this problem Is hypertension in pyelonephritis simply occurring in people who would otherwise get hypertension anyway as a good proportion of the people in this room are going to do does pyelonephritis hasten the onset or increase the severity of the hypertensive process or does pyelonephritis directly cause hypertension in a person who otherwise would never have hypertension? I do not know of any statistics on family history predisposition cold pressor tests and tests of vascular reactivity in people who have been studied for a long period of time to determine whether they get pyelonephritis hyper

tension both or neither Such studies might settle this question which is the crux of the matter

DR DOCK I am glad we started out by giving the impression that pyelonephritis might be a cause of hypertension and ended up by leaving you confused on this issue as well

Epidemiology of Primary Hypertension with Particular Reference to Racial Susceptibility

MARVIN MOSER

White Plains N Y

Conflicting reports regarding the prevalence of elevated blood pressure in various racial groups have been published during the past twenty years Numerous studies have been carried out in an effort to show that the blood pressures in many primitive societies are generally lower than in more complex civilizations[1-4] Reports from China and Africa originally stated that pressures among Orientals and Negroes in these areas were considerably lower than in comparable individuals in the Western hemisphere[1, 5, 6, 7] Comparisons have been drawn repeatedly between these investigations and reports from areas where societies have become more complicated in an effort to link elevation of blood pressure to the "stress of modern civilization

Of particular interest have been the numerous studies originating in Africa that have stressed the marked difference between blood pressures in the African Negro and the Negroes in the United States and Western Hemisphere The most frequently quoted papers in this regard are those of Donnison[1] and Williams who studied natives in East Africa and reported that blood pressures were lower in all ages and both sexes than in comparable groups of whites and Negroes elsewhere It is largely on the basis of these studies that many conclusions have been drawn regarding the effect of civilization upon the blood pressure of the American Negro Numerous other investigators have however reported that blood pressures among primitive peoples and among the natives in Africa are in many instances comparable to levels found in Negroes in other parts of the world Although reliable data are not available in most areas studies from the Belgian Congo Ruanda Urundi Northern Rhodesia and Capetown South Africa suggest that hypertension is not uncommon among the colored and Bantu populations in these countries and that elevated blood pressures do occur in some of the primitive" tribes[8, 9, 10] Both the severity of the hypertension and cerebral vascular complications appear in some cases to be more pro

nounced in the colored than in the whites especially in Capetown South Africa

Several recent investigations of blood pressures in the Negro population of the United States and West Indies also suggest that the previously reported differences between primitive and civilized peoples may not exist in all areas [11, 12] Unfortunately direct comparisons between these African studies and those on Negroes in the United States and in the West Indies are not possible since the latter groups are descendants of the natives of the *west* coast of Africa namely Ghana Liberia and French Equatorial Africa where adequate blood pressure surveys have not been done Isolated reports from Ghana do suggest that in some instances blood pressures rise in the natives after "urbanization" [13]

Many obvious difficulties arise in attempting to compare data from one epidemiological study with that of another since methods of sampling methods of recording blood pressure and local factors differ from one investigation to the next. Definitions of hypertension also differ in various studies and for purposes of comparison it is more useful in most instances to discuss prevalence of elevated blood pressure" without selecting an absolute level and labeling a segment of the sampled population as "hypertensive

Despite these differences and until more reliable information is forthcoming comparisons of the Negroes in the areas thus far studied with those in the United States and West Indies may be of some interest in providing leads for further investigation of the problem of racial susceptibility to elevated blood pressure Further comparisons with blood pressure data recently compiled in Japan and the near East may also shed some light upon this problem

Hypertension has been reported to be common in the Virgin Islands [14] West Indies and Panama[15] among the Negro populations although there is some suggestion in Panama that elevated blood pressure may be secondary to renal disease

Recent studies in the Bahamas may help to clarify some of the conflicting information regarding blood pressure in the Negro race [11] This area lends itself to a long term study of hypertension for many reasons since

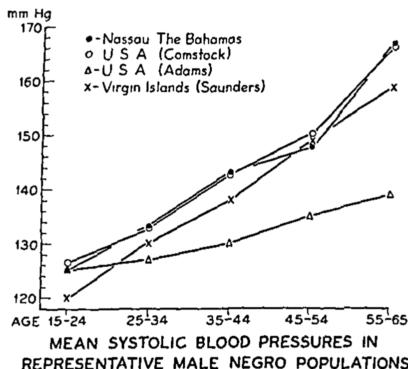
TABLE I COMPARISONS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURES IN THE NEGRO POPULATION OF THE BAHAMAS AND IN THE WHITE POPULATION OF THE UNITED STATES

	MALES		FEMALES	
AGE	U S.A	BAHAMAS	U S.A	BAHAMAS
20 24	123/76	127/77	116/72	127/79
25-29	125/78	132/81	117/74	130/81
30-34	126/79	135/85	120/75	138/86
35 39	127/80	141/86	124/78	147/90
40-44	129/81	144/91	127/80	161/97
45-49	130/82	144/92	131/82	166/99
50-54	135/83	153/94	137/84	166/96
55-59	138/84	169/97	139/84	176/101
60-64	142/85	166/96	144/85	185/100

From Master A M Dublin L and Marks H H The normal blood pressure range and its clinical implications J.A M.A *143* 1464 1950

populations are static they may be studied repeatedly and small island groups may be studied in toto thereby eliminating errors of sampling Tropical diseases and malnutrition factors which may account for the reports of extremely low blood pressures in African populations are not prevalent in this area Comparisons of natives who are living on isolated island groups in a primitive manner may also be made with natives who have been "urbanized and are living in a competitive society with white individuals on the larger islands especially in Nassau Cooperation of the native population is excellent

Preliminary results of this study suggest that blood pressures in all ages and both sexes are higher than in comparable groups of whites in the United

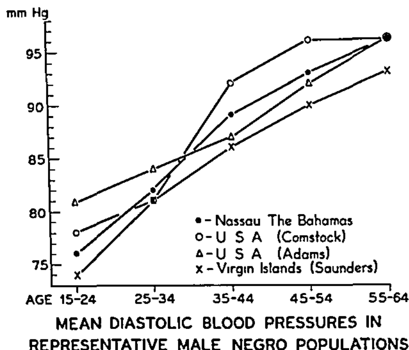


MEAN SYSTOLIC BLOOD PRESSURES IN REPRESENTATIVE MALE NEGRO POPULATIONS

Fig 1

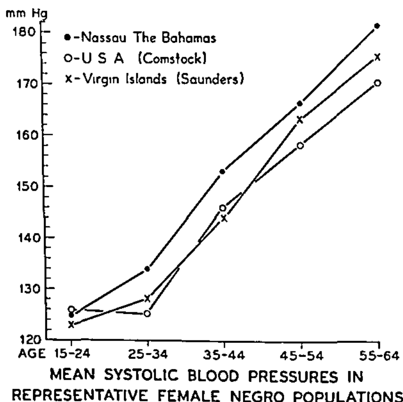
States (Table 1) This applied in both the urbanized" natives who are living on the island of New Providence (Nassau) a resort island with close admixture of the races and in primitive villages on islands such as the Grand Bahama in the northern part of the area Despite the over all elevation of blood pressure on this island an apparent variability in percentage prevalence of elevated diastolic blood pressure (over 100 mm of mercury) from village to village was noted This varied from a high of 35 per cent in one area to a low of 16 per cent in another As far as could be determined these communities were identical regarding mode of living, dietary habits and occupation

Studies of an entire population in the remote village of Rolleville in Exuma a small island in the southern part of the Bahamas further confirmed the fact that there was little difference in mean blood pressure or



MEAN DIASTOLIC BLOOD PRESSURES IN REPRESENTATIVE MALE NEGRO POPULATIONS

Fig 2

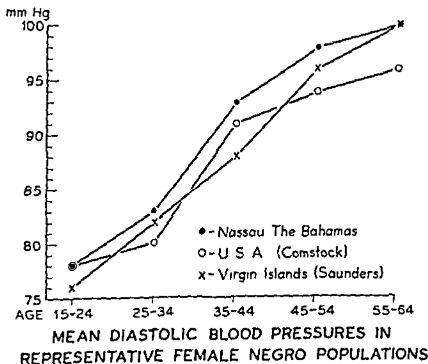


MEAN SYSTOLIC BLOOD PRESSURES IN REPRESENTATIVE FEMALE NEGRO POPULATIONS

Fig 3

percentages of elevated blood pressure in most age groups in the Bahamas regardless of level of civilization

In comparing the results of the studies in the Bahamas with those of Comstock,[16] who recently completed a carefully sampled blood pressure survey of Negroes in a biracial community in Georgia Adams[17] who studied male Negro factory workers in New Orleans and Saunders[14] who reviewed blood pressure data on the Negro population in the Virgin Islands it is apparent that blood pressures are quite similar in all of these studies despite the differences in sampling techniques and in patient groups investigated (Figs 1-4) It will be noted that systolic blood pressures in males in the Adams study are somewhat lower than in the Georgia Virgin Islands or



MEAN DIASTOLIC BLOOD PRESSURES IN REPRESENTATIVE FEMALE NEGRO POPULATIONS

Fig 4

Bahama studies This may be in part due to factors of selection in the former study It is also of interest to note that the prevalence of hyper tension by various criteria is somewhat similar in the Comstock study (U S A) and in those populations investigated in the Bahamas although it will be noted that diastolic hypertension in males is somewhat more preva lent in the latter group (Table 2)

Schrire[10] in Capetown South Africa reported that the over all preva lence of diastolic blood pressures over 100 mm of mercury among the col ored individuals in Capetown was 38 per cent among the Bantus 25 per cent All of these figures are significantly higher than comparable data in white populations in the Western Hemisphere

In considering this data on Negro populations in the southern United States the Bahamas and South Africa the factor of obesity especially in females must be taken into account since in all of these areas extreme over

weight is a common occurrence Considerable error in blood pressure recording especially systolic may be secondary to an increase in arm girth This may account for the apparently "very high" blood pressure levels in females over the age of 40

In a recent review of vascular disease in the Orient Schroeder[18] reported that elevated blood pressure was commonly found in almost every area studied It is of interest to compare data from insurance statistics in Japan and from the white population in the United States with the blood pressures from the Negroes in the Bahamas and the United States (Tables 3 to 6)

TABLE 2

Percent Prevalence of Systolic* and Diastolic** Hypertension Observed in Negroes by Area and Sex

	U S A	Grand Bahamas	Nassau	Rolleville Exuma* *
Systolic Hypertension				
Males	29 8	27 1	29 3	40
Females:	35 0	25 8	33 8	42
Diastolic Hypertension				
Males	4 8	35 4	19 5	37 5
Females:	23 0	34 0	24 2	48 8

* 150 mm/Hg or more
** 100 mm/Hg or more
*** Total adult population (130)

It will be noted that mean blood pressures as well as the percentages of elevated systolic and diastolic blood pressures in both sexes and in most age groups are considerably higher in the Negroes in the United States and in the Bahamas as compared to the whites and Japanese Unfortunately the Comstock data are not reported in the same manner as the other studies but some comparisons can be drawn In the Japanese blood pressures in the older age groups are somewhat higher and in the younger age groups somewhat lower than in the whites in the United States but in general the levels are fairly equal

Comparing these studies presents certain errors since insurance data are selected and may show blood pressure levels somewhat lower than the true mean pressure of a properly sampled population The Bahama data may err in the other direction especially in the older age groups since many of the individuals sampled were from a "patient" population

Contrary to the findings in studies elsewhere in the West Indies and in Panama little evidence was found to suggest that the apparent increase in blood pressure in the Bahamas was secondary to renal disease Preliminary studies in the Bahamas suggested that cardiovascular complications of hypertension were not rare and that elevated blood pressure was not always a "benign" finding Cerebral hemorrhage appeared to be one of the leading causes of death in this area while heart and renal complications were not as common These findings are similar to those reported from many areas in the Orient

TABLE 3 MEAN BLOOD PRESSURE AND INCIDENCE OF ELEVATED BLOOD PRESSURE BY AGE AND SEX IN VARIOUS RACES

Systolic—Males

	UNITED STATES				BAHAMAS		JAPAN****	
	White*		Colored *		Colored***			
AGE	Systolic	% with 150 mm or over	Systolic	% with 150 mm or over	Systolic	% with 150 mm or over	Systolic	% with 150 mm or over
20 24	122 9	3 9	128 5	NOT	127	11 59	116 2	
25 29	125 1	3 8			132	18 3	118 6	
30-34	126 1	5 7	132 9	LISTED	135	28 8	119 8	0 87
35-39	127 1	7 3			141	33 9	122 2	2 2
40 44	129 1	9 7	142 8	IN	144	40 0	125 7	5 2
45 49	130 0	13 4			144	39 1	130 1	10 7
50 54	134 5	20 2	150 6	STUDY	153	48 7	136 5	20 6
55-59	137 8	26 3			169	77 7	140 3	30 1
60 64	141 8	34 9	166 7		166	69 2	145 4	41 9

* Master et al
* Comstock
* Moser et al
**** Schroeder

TABLE 4 MEAN BLOOD PRESSURE AND INCIDENCE OF ELEVATED BLOOD PRESSURE BY AGE AND SEX IN VARIOUS RACES
Diastolic—Males

AGE	UNITED STATES White* Diastolic	UNITED STATES White* % with 100 mm or over	UNITED STATES Colored Diastolic	UNITED STATES Colored % with 100 mm or over	BAHAMAS Colored Diastolic	BAHAMAS Colored % with 100 mm or over	JAPAN Diastolic	JAPAN % with 100 mm or over
20 24	76 0	1 2	77 7	NOT	77	4 3	69 6	
25 29	77 8	1 8	81 1		81	8 4	71 2	
30 34	78 5	1 7		LISTED	85	18 6	72 6	0 5
35-39	80 4	4 3	91 5		86	26 7	74 8	1 5
40 44	81 2	3 8		IN	91	27 7	77 3	3 3
45-49	82 0	7 7	96 2		92	34 7	79 9	6 4
50 54	83 4	8 6		STUDY	94	43 5	82 7	10 6
55 59	84 0	12 7	95 9		97	51 8	84 6	14 3
60-64	84 5	14 9			96	44 2	86 2	18 5

Master et al
Comstock
* Moser et al
Schroeder

TABLE 5 MEAN BLOOD PRESSURE AND INCIDENCE OF ELEVATED BLOOD PRESSURE BY AGE AND SEX IN VARIOUS RACES

Systolic—Females

	UNITED STATES				BAHAMAS		JAPAN***	
	White*		Colored*		Colored **			
AGE	Systolic	% with 150 mm or over	Systolic	% with 150 mm or over	Systolic	% with 150 mm or over	Systolic	% with 150 mm or over
20 24	115 7	1 3	125 9	NOT	127 0	13 6	112 9	
25-29	116 8	1 5			130 0	14 8	116 0	
30-34	119 8	3 4	124 9	LISTED	138 0	32 3	116 2	0 8
35-39	123 9	5 3			147 0	41 1	118 3	1 4
40-44	127 0	9 6	146 3	IN	161 0	60 3	122 6	4 2
45-49	130 6	17 3			166 0	67 0	127 8	9 8
50 54	137 3	28 3	158 2	STUDY	166 0	72 0	133 8	17 8
55 59	138 5	29 7			176 0	75 0	139 7	27 5
60 64	144 0	39 8	170 0		185 0	88 0	147 0	43 4

* Master et al
Comstock
** Moser et al
*** Schroeder

TABLE 6 MEAN BLOOD PRESSURE AND INCIDENCE OF ELEVATED BLOOD PRESSURE BY AGE AND SEX IN VARIOUS RACES

Diastolic—Females

	UNITED STATES				BAHAMAS		JAPAN **	
	White		*Colored*		*Colored* *			
AGE	*Diastolic*	*% with 100 mm or over*	*Diastolic*	*% with 100 mm or over*	*Diastolic*	*% with 100 mm or over*	*Diastolic*	*% with 100 mm or over*
20 24	71 7	3	78 3	NOT	79	9 0	67 2	
25 29	73 7	1 2	80 1		81	14 8	68 2	
30 34	74 9	1 9		LISTED	86	26 4	70 0	0 5
35 39	78 0	2 9	90 5		90	25 0	72 4	0 9
40 44	79 5	4 7		IN	97	48 1	74 9	2 4
45 49	81 5	8 9	93 6		99	52 0	78 0	5 2
50 54	83 5	12 0		STUDY	96	41 8	81 0	8 5
55 59	83 5	11 0	96 6		101	55 0	83 2	12 8
60 64	85 0	15 2			100	51 0	86 0	18 6

Master et al
Comstock
Moser et al
Schroeder

Attempts to relate the incidence of elevated blood pressure with other factors commonly believed to be involved with pathogenesis have been largely unsuccessful in all of the studies reported to date Correlation of *disease states such as syphilis with hypertension have been reported* but the evidence is not convincing

Schroeder was unable to find a single factor of significant" importance in the Orient Emotional stress, "Westernization" and dietary habits did not appear to explain the prevalence of elevated blood pressures in this area Renal disease did not appear to be of primary importance Sodium chloride intake varied considerably from 3 to as high as 25 gm a day in different countries but the data was fragmentary and did not appear to correlate with the varying prevalence of hypertension

Efforts to determine whether the apparently higher levels of blood pressure in the Negro race are a result of heredity or secondary to some environmental factor or factors have been made repeatedly It would appear at present from all of the studies reviewed that the explanation is not a simple one and that stress or "urbanization" can no longer be accepted as *the* causative factor The conclusion from even the fragmentary data available that blood pressure in the Negro race is higher regardless of area studied regardless of urbanization or level of civilization—in fact that there is a true "racial susceptibility" to hypertension—might be drawn Other factors must be ruled out however before this premise can be accepted It may be that in one area such as the United States factors of stress or civilization are important whereas in other areas such as the Bahamas or in portions of Africa where blood pressure apparently is high among the *Negroes despite their primitive surroundings and apparent lack of interracial stress* other factors may be operative

Efforts to elaborate on these other possibilities in the Bahamas have as yet been unsuccessful Although preliminary evidence suggests that salt intake is high in these peoples sufficient data are not as yet available to clarify the role of a high salt intake in hypertension Excretion studies suggest that intake varies from 12 to as high as 25 gm of sodium chloride daily in some areas but the marked variability of prevalence of elevated blood pressure from community to community with the same dietary habits suggests that hereditary factors may be of more importance High salt ingestion superimposed upon a hereditary" or racial susceptibility may of course be of significance

CONCLUSIONS

From the foregoing data it would appear that there is a distinct racial difference in *levels of blood pressure although more careful population* studies must be done before final conclusions can be accepted Elevated blood pressures and an increased prevalence of hypertension by any of the accepted definitions is apparently more common in the Negroes than in white or Oriental populations Despite the marked differences in techniques employed in each of the studies compared i e use of a "patient population for study in one sampling of a healthy population only in another and a mixed group in the third this conclusion appears to be warranted.

Further errors in the results of these studies might also arise from the recording and reporting of casual and not the so called" basal blood pres

sure since the marked variability in pressure levels from day to day and during the same day in the same individual is well recognized Comstock in his review presented data that suggested that in a large scale study of blood pressure many of these errors might tend to cancel out The trends" of all of the available surveys but perhaps not the absolute values would appear to be useful for comparison With these reservations in mind certain other cautious conclusions may be justified at this time

1 Blood pressures in African natives contrary to the few isolated reports from Kenya and areas on the east coast of Africa apparently are as high or higher than blood pressures in white individuals In many instances blood pressures in the Africans are comparable to the usually elevated levels noted in the American Negro and in the colored individuals in the West Indies From available data there is a suggestion that cardiovascular disease and complications of elevated blood pressure especially cerebral complications are not uncommon among the Negroes and that blood pressure elevation is not a "benign" finding Cerebral complications are also frequently noted in the Oriental race

2 Recent data from Africa and the Bahamas suggest that elevation of blood pressure in the Negroes occurs both in primitive and in civilized surroundings and is not directly related to "urbanization" although in some areas this may be a contributing factor Data from the Orient also appear to support this view

3 Comparisons of blood pressure of colored individuals in the United States the West Indies and Capetown South Africa white individuals in the United States and Japanese subjects suggest that there may be a racial susceptibility" of the colored race to elevation of blood pressure

4 Although salt intake appears to be high in some areas with a high prevalence of hypertension in the Orient and in the Bahamas the absolute correlation of this finding with elevated blood pressure must await further study Hereditary factors may be of more importance in explaining the variability of prevalence in different areas with apparently similar salt intake

5 Additional genetic and long term studies are needed in carefully sampled Negro populations in order to more clearly define the apparent "racial susceptibility of the colored race to hypertension

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Hypertension in the Orient*

HENRY A SCHROEDER

Dartmouth Medical School and Brattleboro Retreat

There is a prevailing opinion that arterial hypertension is uncommon or rare in certain Oriental peoples especially Chinese and that their blood pressures are lower than those of European races Therefore a survey was made in 1956 at fifteen leading medical schools in eleven cities of seven Oriental countries to ascertain whether or not this opinion was correct It was not Hypertension and its consequences were found to be clinical problems in all cities studied and were serious ones in most

Three methods were used to determine incidences Insurance or survey statistics autopsy statistics and hospital or clinic admissions Although the data were by no means complete, two of these methods were available in each country Statistics were considered to be reasonably reliable at each medical center Pathologists internists and cardiologists familiar with the disease by reason of specialized training received at European or American institutions were consulted

Insurance or survey statistics were available for Japan (269 583 male and 45 392 female life insurance applicants) Taipei Taiwan (6 421 male and 3 308 female residents on a house to house survey) Agra India (2 431 male and 1 875 female normal persons in a house to house survey) Delhi India (486 male industrial workers in a cloth mill) and Najafgarh India (222 male and 344 female normal persons living in a small village) In Table 1 are shown the results in three of these areas Obviously hyperten

*Prepared under a grant in aid from the American Heart Association

TABLE 1 INCIDENCE OF ARTERIAL HYPERTENSION IN JAPANESE LIFE INSURANCE APPLICANTS CHINESE OUT PATIENTS IN TAIPEI AND NORMAL INDIANS (PER CENT) COMPARED TO THAT IN 75 000 AMERICANS (DUBLIN AND MARKS)

	MALE				FEMALE				MALE	FEMALE	MALE	
	United States		Japan		United States		Japan		Taipei		Delhi	Villagers
Age	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic				
20	3 9	1 2	0	0	1 3	0 3	0	0	1 3	1 2	4 8	2 0
25	3 8	1 8	0	0	1 5	1 2	0	0	1 6	2 7		
30	5 7	1 7	0 87	0 5	3 4	1 9	0 8	0 5	2 8	3 8	5 2	6 9
35	7 3	4 3	2 0	1 5	5 3	2 9	1 4	0 9	7 7	7 2		
40	9 7	3 6	5 2	3 3	9 6	4 7	4 2	2 4	9 8	13 0	10 0	8 7
45	13 4	7 7	10 7	6 4	17 3	8 9	9 8	5 2	15 7	13 7		
50	20 2	8 6	20 6	10 6	26 3	12 0	17 8	8 5	19 5	22 1	8 7	12 5
55	_8 3	12 7	30 1	14 3	29 7	11 0	27 5	12 8	17 1	14 3		
60	31 9	14 9	41 9	18 5	39 8	15 2	43 4	18 6	12 3	11 0		
65			55 8	16 8					11 4	10 5		

Japanese Chinese and Americans Systolic > 150 Diastolic > 100 mm Hg Indians > 140/90 mm Hg In each age group the figure applies to the age up to the next group shown

sion is present in each and is probably more frequent in Japanese than in Americans for reasons to be discussed later

The mean blood pressure of Japanese below the age of 30 at which age there is little or no hypertension is about 7 mm systolic and 6 mm diastolic lower than in Americans of comparable age The mean blood pressure of normal Chinese in Taipei is almost superimposable age for age upon that of Japanese The mean blood pressure of Indians of both sexes in Agra is lower by 3 or 4 mm Hg systolic and 1 or 2 mm Hg diastolic than that of Americans up to the age of 60 in a small number of Indians in Delhi it appears not to increase with age appreciably

These data must be examined from the two opposing points of view now prevalent in this country (a) blood pressure increases normally with age (truly a unique biological phenomenon) and (b) normal blood pressure is established early in adult life but the increasing frequency of hypertension with age causes the means to rise In accord with the first hypothesis these data suggest that hypertension is more common in older and less common in younger Japanese than in comparable groups of Americans According to the second hypothesis which is based on decreasing numbers of normotensive persons as age increases these data suggest that there is *considerably* more hypertension in Japanese than in Americans for high standards of American normality (150/100 mm Hg) were used in the Japanese statistics and the blood pressures of normal young Japanese are lower than those of Americans Furthermore the normal levels of blood pressure in Japanese Chinese (Taiwanese) and Indians appear to be comparable to and somewhat lower than those of Americans

TABLE 2 INCIDENCE OF ARTERIAL HYPERTENSION IN CONSECUTIVE AUTOPSIES IN PATIENTS OVER THE AGE OF 40 (PER CENT)

CITY	NUMBER OF CASES	PRIMARY HYPERTENSION	SECONDARY HYPERTENSION
Manila	104	37	6
Bangkok	114	5	5
Lucknow	100	9	2
Bombay	130	7	4
Beirut	110	18	10
Bombay	850	6 1	

Larger study all ages

Consecutive autopsies were examined in each of five cities Manila Bangkok Lucknow Bombay and Beirut, for the presence of non valvular cardiac hypertrophy and arteriolar nephrosclerosis (primary hypertension) or organic renal disease (secondary hypertension) in persons over the age of 40 In Table 2 are shown the results There appeared to be especially high incidences in Manila and Beirut and in no city were the pathological manifestations of the disease absent

Confirmation for the statement that arterial hypertension and hypertensive vascular disease is a serious clinical problem in most cities in the Orient is found by an analysis of hospital admissions on which the diagnosis was made In Table 3 are shown these data While clinical interest in the disease may vary from place to place and diagnostic criteria vary likewise these data were considered the best available the incidences may have

TABLE 3 INCIDENCE OF ARTERIAL HYPERTENSION IN VARIOUS TEACHING HOSPITALS (PER CENT OF MEDICAL ADMISSIONS)

CITY	NUMBER OF ADMISSIONS	PER CENT HYPERTENSION
Taipei	122 828–OPD	1 3
Taipei	18 984–OPD	2 1
Hong Kong	10 000–Chinese	7 8
Manila	8 470	8 7
Bangkok	8 808	2 9
Agra	12 611	1 4
Lucknow	4 444	1 4
Bombay	5 303	2 2
Beirut	14 486	9 8
St Louis	40 420	15 9

Including cerebral hemorrhage

been higher than indicated in some areas but were certainly not lower In all hospitals only patients with symptomatic hypertension were admitted

Of the secondary manifestation of chronic hypertension further evidence for the frequency and severity of the disease in the Orient was observed Japan has the highest apoplexy rate in the world vascular lesions of the central nervous system most of which are cerebral hemorrhage have long been the first cause of death (135 9 per 100 000 in 1955) over twice the death rate from heart diseases (60 4 in 1955) In Taipei the death rate for vascular lesions of the central nervous system was 51 0 per 100 000 in 1954 The data available are shown in Table 4 Hypertension appeared to affect the vessels of the brain with decreasing potency from Japan westward Malignant hypertension was common in all areas more common than in Europe or America from these data

No correlation other than with poor nutrition appeared with any of the parameters considered to be of etiologic importance in the West Unless all

TABLE 4 INCIDENCES OF SECONDARY MANIFESTATIONS OF HYPERTENSION IN HOSPITAL PATIENTS MEDICAL ADMISSIONS

AREA OR CITY	CEREBRAL HEMORRHAGE, PER CENT OF ADMISSIONS	MALIGNANT HYPERTENSION PER CENT OF HYPERTENSION	HYPERTENSIVE HEART DISEASE PER CENT OF ADMISSIONS	REMARKS
Japan	136/100 000			Death rate vascular lesions C N S
Taiwan	51/100 000	5 0		Death rate vascular lesions C N S
Hong Kong				
Chinese	2 25	16 6		
(autopsies)		(1.2)	(2 1)	Per cent of 3 200 autopsies
Manila				
Filipinos	1 7	7 3		
Chinese	4 4			
Bangkok	2 4	14 8	1 9	
Agra	1 8	13 0		
Lucknow	0 45			
Bombay	0 37	7 9	1 0	
Beirut	0 37		6 3	

dwellers in cities are tense emotional tension in the enervating tropics (Taiwan Hong Kong Manila Bangkok India) was not an obvious factor The dietary intake of sodium chloride did not appear to correlate with the presence or absence of hypertension although actual measurements were available only in Japan (approximately 10 gm per day) and Manila (mean 9 gm, range 3 to 17 gm per day) It was estimated to be very low in Thailand and India and very high in Northern Japan

The caloric intakes of the urban populations from which the data were drawn were in general adequate although diets were often low in one or more vitamins Animal protein was seldom included in most of the dietaries vegetable and fish protein were usually available It is almost certain that a study of malnourished people would have yielded different results

SUMMARY AND CONCLUSIONS

Arterial hypertension and its consequences were found in all of eleven Oriental cities and were serious clinical problems in most areas The impression that hypertension is rare or absent in some Oriental races was unconfirmed and should be discarded There is probably more hypertension in Japanese than in Americans

The mean blood pressure of those Oriental people on whom surveys have been made is slightly lower than that of American urban dwellers It would appear that Oriental urban populations receiving adequate calories are uniformly subject to hypertension and hypertensive diseases regardless of race

REFERENCE

The full data and their sources from which this discussion was taken are found in Schroeder H A Degenerative cardiovascular disease in the Orient I Atherosclerosis II Hypertension J Chron Dis 8 287-333 1958

High Arterial Pressure as a Primary Cause of Hypertensive Vascular Lesions*

G M C MASSON and A C CORCORAN

Cleveland Clinic Foundation

Gull and Sutton[1] in 1872 defined the concept of the primacy of "arterio capillary fibrosis" as the cause of hypertension in the "morbid state called chronic Bright s disease with contracted kidney " Mahomed in 1879 came to the opposite conclusion [3] He was primarily a clinician and was one of

* The investigations reported in this paper were supported by a grant from the National Heart Institute National Institutes of Health

the first to measure arterial pressure and correlate it with clinicopathologic changes Unfortunately he died while still a young man and was thus prevented from convincing the medical public the authority of the older presumably wiser men prevailed

The demonstration by Goldblatt in 1934[4] that partial occlusion of the main renal artery could cause hypertension seemed to support the view that primary nephrosclerosis if not diffuse "arterio capillary fibrosis might be the true event in hypertension This concept received further support from the observations of Moritz and Oldt (1937)[5] who showed that people who died of a complication of hypertension consistently showed signs of nephro sclerosis

The experiments of Wilson and Byrom[6 7 8] Floyer[9] and Selye[10] repre sent a large body of evidence to show that hypertension causes and that relative normotension or hypotension tends to prevent nephrosclerotic le sions in rats These unite in suggesting that high arterial pressure as such is a primary if not the only significant factor in the pathogenesis of these lesions Unfortunately the design of these experiments was such that the associations observed were definable for the most part only in qualitative terms A direct approach to the problem has been made by Byrom and Dodson[11] Masson Corcoran and Page[12] and Schaffenburg and Goldblatt[13] but with discordant results These are considered below

Quantitative associations have been reported between the degree of arterial hypertension and the severity of hypertensive vascular disease in small groups of rats with hormonal hypertension treated with hydralazine and/or reserpine[14] This association has been controverted in rats with renal hypertension by Koletsky[15] who used Dibenamine as an antihypertensive drug More recently we have defined a quantitative association of high arterial pressure and arterial lesions in rats with hypertension due to partial renal infarction some of which were treated with hydralazine[16]

Those who are not convinced of the association between pressure and lesions have drawn attention to other factors which may be contributory and are sometimes contradictory as for example both the presence and the absence of intact renal tissue These concepts particularly apply to the acute fulminant lesions of malignant hypertension and not those of classic hypertensive vascular disease Indeed Perera believes that he has demon strated clinically a condition of "Hypertensive Disease without Hyper tension"[17]

Thus the controversy has extended over 80 years with varying trends and often with more conviction and acerbity than evidence The data re ported below together with our previous experience[18] and with observations on the course of severe human hypertension as affected by long term treat ment with effective antihypertensive drugs[19] have convinced us of the asso ciation between pressure and lesions and of the primacy of pressure in causing lesions in various hypertensive states

As noted above results of direct experiments have not been concordant Byrom and Dodson[11] found that forced manual intracarotid injections of 2 ml saline repeated 10 to 15 times caused focal arterial necrosis especially in the renal vascular bed Arterial pressure registered by a mercury manometer increased 80 to 90 mm Hg Using a mechanical device constructed by Mr F Olmsted of this Division we confirmed these findings They are described



Fig 1 Effects of forced injections into the carotid artery on pressure in the femoral artery Injection of 2 5 ml of Ringer s solution under a pressure of (1) 0 7 kg per cm[2] and (2) 2 kg per cm[2] Injection of 5 ml under a pressure of (3) 0 7 kg per cm[2] and (4) 2 kg per cm[2] *Time intervals (I) represent duration of injections (Figs 1 to 3 are* reprinted from Masson et al Rév Canad de Biol *10* 309 332 1951)

here in some detail largely because they were *originally presented in a* journal not widely circulated in this country

TECHNIQUE

The injection apparatus consisted of a 50 ml syringe enclosed partly in an air tight glass cylinder communicating through a regulating valve with compressed nitrogen Under these conditions it was possible to regulate accurately the pressure in the air chamber and therefore the flow of fluid from the syringe Using a #22 needle inserted into the carotid artery the critical pressure was found to be 2 kg per cm[2] the flow was then 240 ml per minute Above this value fatal hemorrhages occurred in the aorta Since a mercury manometer was ill adapted to exact measurements we used a capacitance manometer cannulated to the femoral artery, it was found that our mechanical device could yield equal reproducible increases in pressure



Fig 2 Kidney from a rat sacrificed 24 hours after forced injections Severe distention of the wall of an intralobular artery *Edema and hemorrhages of the intima resulting in* partial obliteration of the lumen Interstitial hemorrhage and edema Trichrome × 200

Figure 1 shows that each injection is followed by an immediate and rapid rise in arterial pressure which is not maintained during the entire duration of the injection For this reason we decided that it was more important to increase the number rather than the volume of the injections We have injected doses of 2.5 to 5 ml every 2 minutes up to a total volume of 80 ml Rats were sacrificed up to 1 week after each series of injection Blood pressure recorded in some of them by tail plethysmography showed a regular increase up to 180 mm Hg from a base line of about 100 mm Hg during the succeeding 5 days followed by a fatal abrupt fall The lesions restricted to the kidney consisted of hemorrhages excessive distention of arteries and arterioles edema of the intima resulting in partial obliteration of the lumen and focal necrosis of the muscularis (Figs 2 and 3) These observations are essentially in accordance with those of Byrom and Dodson[11] but differ from the more recent ones by Schaffenburg and Goldblatt[13] Like Byrom and



Fig 3 Kidney from a rat sacrificed 48 hours after forced injections Hemorrhages and fibrinoid necrosis without distention of the arterial wall Trichrome × 200

Dodson they injected fluid manually in amounts of 2 ml repeated at intervals of 1 minute up to a final volume of 30 ml They reported maximum arterial pressure rises up to 194 mm Hg above the basal level However since these measurements were made with a mercury manometer connected to the aorta these high values may reflect in part the momentum of the mercury column Thus although the conditions of their experiments resemble those of Byrom and Dodson allowing for differences in manually controlled injections Schaffenburg and Goldblatt failed to detect any pathologic vascular changes Whatever the significance of the results we recognize the basically unphysiologic conditions inherent in this type of experiment

A clearer demonstration of the relationship between pressure and vascular disease has been provided by the use of hypotensive agents in rats with infarcted kidneys

Renal infarction was performed in one kidney by the method of Loomis [7]

and was associated with contralateral nephrectomy Hydralazine (Apresoline) was selected as a potent antihypertensive agent A series of preliminary experiments defined that it could sustain a persistent antihypertensive effect when added to drinking water (40 mg per liter) The fact that a maximally effective dose was thus given was confirmed by the failure to demonstrate a further decrease in arterial pressure when after 7 days of oral treatment, a test dose of hydralazine was given by gavage

RESULTS

Two series of experiments were done In the first one we were concerned with the effects of hydralazine induced control of hypertension on the acute lesions developing during the first 7 to 15 days after operation and



Fig 4 Healing process in a pancreatic artery from a rat with renal infarction kept without treatment during one month and then treated with hydralazine during the second month The dark central core represents the original limits of a vessel which is well repaired The cuff is formed of sclerosed tissue containing blood pigments PAS stain × 100 (Figs 4 and 5 are reprinted from Masson et al Am J Path 34 817 833 1958)

in the second on the effect over periods of one and two months including the effect of one month of hydralazine treatment on lesions which had developed in the absence of treatment during the first month

Series I Particular attention was paid to extrarenal vascular disease because of the possibility of confusing renal lesions consequent on infarction with those attributable to hypertensive disease In the absence of treatment extrarenal vascular lesions primarily splanchnic were found in some two-thirds of the animals Treatment with hydralazine from the time of operation maintained arterial pressure within normal limits in most animals and decreased the incidence of extrarenal lesions from 66 to 18 per cent However in these experiments as in Series II hydralazine was found not to protect against myocardial hypertrophy

Series II In these as in Series I oral hydralazine prevented the expected rise of arterial pressure for periods up to 2 months When at the end of one month of treatment hydralazine was discontinued pressure rose promptly to hypertensive levels lesions which in similarly treated animals killed at the end of one month had been inhibited developed in florid form by the end of the second month Animals continuously under treatment for either one or two months showed a decreased incidence of lesions as compared with untreated hypertensive controls Gross splanchnic arteritis was present in the untreated (one or two months) hypertensive controls and in animals which had been treated for one month and then left untreated *during the second month similar healed lesions occurred in animals allowed to be hypertensive for the first month and treated during the second*



Fig 5 Kidney from a rat with renal infarction treated with hydralazine for two months Small renal artery showing progressive vascular disease with deposition of Schiff positive material and thickening of the wall in spite of treatment Vascular disease was absent in the extra renal vascular beds PAS stain × 220

(Fig 4) Throughout as in the brief experiments there was a strong association between blood pressure as measured by tail plethysmography and the presence absence state of regression or activity of the extrarenal vascular lesions *The sensitivity of the renal vascular bed was demonstrated by* the presence of unexpected lesions of progressive damage to large arterioles and small arteries in some of the animals maintained under continuous treatment with blood pressures within the range of normal (Fig 5) Possibly some of these may have been transiently hypertensive at some time during treatment The results of our direct injections suggest that only 20 to 30 such episodes each lasting less than a minute might result in renal lesions As in Series I cardiac hypertrophy was not prevented by hydralazine treatment *In this the experience is similar to that of the clinical treatment of hypertension with hydralazine* [1]

NEUROGENIC HYPERTENSION

One disturbing inconsistency in the association between hypertension and arterial lesions is the fact that most workers have failed to demonstrate such lesions in the course of neurogenic hypertension due to buffer nerve resection in dogs [23, 4] Lesions have been described by Daman et al [3] in dogs maintained for periods up to 3½ years these occurred primarily in the glomerular basement membranes *They do not seem to us characteristic* of diffuse nephrosclerosis Further it should be remembered that dogs with moderate degrees of renal hypertension may be maintained for periods up to 6 years without developing recognizable renal vascular lesions in the kidney contralateral to that causing the hypertension [6] Thus it appears that the dog is more resistant to the nephrosclerotic effects of arterial hypertension than the rat and possibly the human being

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The Relationship of Hypertension to Atherosclerosis

QUENTIN B DEMING and MARIE M DALY
College of Physicians and Surgeons Columbia University

In humans the hypertensive state is accompanied by an increased incidence and severity of atherosclerosis This atherosclerosis is responsible for a large part of the morbidity and mortality of hypertensive disease The mechanism by which hypertension intensifies atherogenesis is not established There is some evidence derived from the location of lesions suggesting that the effect may be a local one on the vessel wall perhaps related directly to the effects of local pressure or turbulence of the blood

The experimental work discussed here is concerned with two questions First is the hypertensive state associated with generalized changes in lipid metabolism and second are there demonstrable changes in the metabolism of arterial wall in the hypertensive state which might affect local tissue degeneration and/or lipid deposition?

1 It has been shown[1] that the ingestion by albino rats of a diet containing 4 per cent cholesterol 1 per cent cholic acid and 0 5 per cent thiouracil results in the development of atherosclerotic lesions at the base of the aorta and in the coronary arteries In addition despite the fact that endogenous cholesterol synthesis (as measured by incorporation of C^{14} labeled acetate) appears to be arrested ingestion of this diet results in gross increases of cholesterol beta lipoprotein and total lipid in the serum and gross increases in the cholesterol content of both liver and carcass

If experimental hypertension is produced in rats on this diet all of these changes are intensified The hypertensive animal has more atherosclerosis higher concentrations of the various lipids in its serum and a greater total

content of cholesterol in its liver and carcass than the normotensive animal has There is a positive correlation between the blood pressure and both the extent of atherosclerosis and the concentration of cholesterol in the serum

In the rat on this diet therefore it appears that there may be changes in general lipid metabolism associated with the hypertensive state Whether these changes are related to the intensification of atherogenesis has not been demonstrated nor has this effect on lipid metabolism yet been demonstrated in euthyroid animals in animals on a normal cholesterol intake or in humans

2 Aortas isolated from albino rats on a regular Purina Chow diet were used for the studies of arterial metabolism discussed here Aorta contains a large amount of extracellular material (collagen elastin and membranes) which does not participate measurably in respiratory activity

The oxygen consumption of aortas isolated from hypertensive rats is *higher than that of aortas from normotensive rats whether the comparisons* are calculated on the basis of total nitrogen content of the tissue samples or on desoxyribonucleic acid content (used as a measure of the relative number of cells present)

Cytochrome oxidase activity of aortas from hypertensive animals is higher than that of aortas from normotensive animals when calculated on the basis of total nitrogen content or when calculated on the basis of non collagen non elastic nitrogen In the latter instance while the difference is still significant it is smaller than in the former instance suggesting that some of the increase in cytochrome oxidase activity might be accounted for by the increased proportion of muscle in the aorta of the hypertensive animal

Aortas of hypertensive animals contain a higher proportion of non elastic non collagen nitrogen (presumably representing muscle cells) than aortas of normotensive animals a change assumed to be a concomitant of medial hypertrophy

It appears therefore that there are changes in the metabolism of artery wall in the hypertensive animal The metabolic changes shown probably occur mainly in the media of the vessels but they might have an indirect influence on the intima What other metabolic changes may occur and whether one or more of them is directly related to the intensification of atherogenesis or to local or systemic changes in lipid balance remain to be demonstrated

In order to facilitate interpretation of these results answers are being sought *to the following questions*

1 *Is the increased severity of atherosclerosis* in the hypertensive animal dependent on the additional increment in the serum cholesterol concentration?

2 What is the source of the increased cholesterol in the serum and tissues of the hypertensive animal?

3 Can the metabolic changes in arterial wall of hypertensive animals account directly for local deposition of lipid or local tissue necrosis?

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Are Malignant Hypertension and Benign Hypertension Different Diseases?

JOSEPH H HAFKENSCHIEL
The Lankenau Hospital Philadelphia

This review covers the period from 1928 to 1958 and attempts to provide a framework upon which further discussion might be constructed This should allow the reader to appreciate the many gaps remaining in the fund of knowledge concerning the genesis and course of primary disturbances of blood pressure regulation

I HISTORICAL REVIEW WITH ORIENTATION OF THE AUTHOR

Malignant hypertension has been defined "A clinical phase rarely occurring *de novo* more often appearing after a primary or secondary hypertension characterized by diastolic hypertension and by accelerated and progressive renal damage usually (but not necessarily) accompanied by papilledema often by retinal hemorrhages and exudate and giving rise to early death from the uremia unless the course is terminated along the way by complicating brain or heart damage"[1]

Histologically the changes of a widespread proliferative endarteritis and necrotizing arteriolitis are accepted as being a characteristic feature of the accelerated or "malignant" form of hypertension

Goldblatt in his editorial "Pathogenesis of Malignant Hypertension" comments that there "has been lack of agreement about the nature and pathogenesis of the necrotizing arteriolar lesion that is found in the kidneys and other organs and that is regarded by most investigators as a pathognomonic feature of malignant hypertension"[3]

This lack of agreement concerning the significance of the pathologic alterations and the genesis of malignant hypertension was brought to my attention in 1938-39 when as a second year medical student I was studying pathology with W G MacCallum My teacher stated "Fahr has maintained for some years the existence of a particularly severe form of renal disease which he calls maligne nephrosklerose "[4] The chapter on nephritis in his textbook is concluded as follows We are left as we began with only rudimentary ideas as to the cause of nephritis clear only in the case of a few infections and poisonings with no definite knowledge of the relation between general metabolic processes and defects in the function of the kidneys in the explanation of the chemical changes in the blood and urine in nephritis with no comprehension of uremia and only the vaguest notions of the causes of arterial hypertension"

As to the clinical picture in man Bright, about one hundred years earlier and seventy five years before a blood pressure measuring device was con

structed to detect this presumed that cardiac hypertrophy was secondary to kidney disease. This myocardial change was thought to be the result of increased work required to force blood through a vascular system constricted because of the presence of irritating humoral substances resulting from impaired kidney function.[6] In 1914 the physician Volhard described with Fahr their clinicopathological investigation of hypertension and suggested that malignant hypertension could evolve naturally from untreated essential hypertension. Wagener and Keith described the retinopathy and emphasized the serious prognosis and in 1928 for the first time (in the English speaking world) as far as I can determine used the phrase malignant hypertension to show the unfavorable course of patients with very high blood pressure.[7] Those with the poorest prognosis were the ones with changes in the fundi such as papilledema, exudates and hemorrhages associated with high diastolic pressure and impaired renal function.

The atmosphere of MacCallum's department was that of a laboratory of experimental medicine. Rich and Blackman were interested in post mortem material from the Johns Hopkins Hospital services that would enable them to correlate the clinical syndrome of malignant hypertension with changes in the major renal arteries and the arterioles of the other kidney. In 1939 Blackman reported finding atherosclerotic plaques projecting into the renal arteries in 86 per cent of 50 cases of essential hypertension and pronounced stenosis in 25 per cent of these patients.[8] Studies of this type were continued after MacCallum's death and in 1954 Howard together with the pathologist Berthrong described six cases with vascular lesions of one kidney in which a severe hypertension was relieved by removing the kidney.[9]

Claude Bernard suggested that experimenting physicians should not be mere physiologists waiting with folded arms for experimental medicine to be established scientifically before taking action in behalf of their patients.[10] The experiments of Goldblatt initiated in 1932 were the beginning of a very intensive period of investigation in all the disciplines that make up experimental medicine,[11] having been the stimulus for the hypertension research in MacCallum's department. Many problems have been elucidated in the fields of physiology including neurophysiology, biochemistry, pharmacology, pathology, internal medicine in general and in some of its subspecialties such as neurology, psychiatry and surgery. To recapitulate briefly I should note that Page and Heuer in 1934 embarked upon the treatment of essential and malignant hypertension by section of the anterior nerve roots.[1] In 1937 Butler reported the effects of nephrectomy in children who had unilateral pyelonephritis with associated vascular disease and high blood pressure.[13] The next year Smithwick began thoracolumbar sympathectomies[14] and in 1939 Keith and his coworkers presented the survival experience of patients with high blood pressure divided into groups according to retinopathy.[15] Keith recently stated that in 1939 he avoided the use of the term malignant hypertension, referring to those patients having the worst prognosis as "group IV" cases.[16] Confirmation of similar survival results in untreated patients has been provided by Smithwick (1951) and Kincaid-Smith, McMichael and Murphy in 1958.[17] Despite Keith's good intentions in 1939 the phrase malignant hypertension remains with us and even second year medical students today understand what are the characteristic features of the clinical syndrome. What is different now compared to

twenty five years ago before an experimental laboratory counterpart of malignant hypertension had become available is that something can be done for some patients with severe diastolic high blood pressure who are not yet azotemic

My topic relates to the diversity of opinion about the pathogenesis of malignant hypertension Some today as MacCallum did consider it to be a form of essential hypertension not of renal origin but marked by renal excretory impairment occurring as a late or terminal manifestation others such as Goldblatt believe that the malignant phase like the benign is primarily and even more obviously of renal origin [18] Perera has presented his

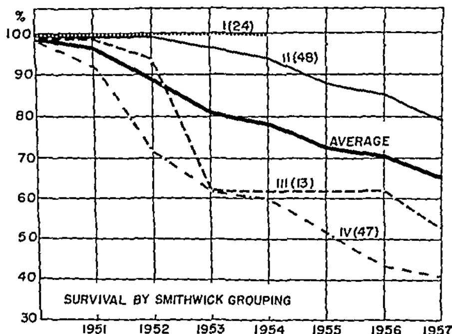


Fig 1 Survival data in 132 patients with primary hypertension as of 1957 Some of these patients were seen as early as 1946 all of these 77 men and 55 women having been seen in 1952 or before The patients were given a prognosis rating using the criteria of Smithwick at the time of the initial baseline examination The graph shows that only 41 per cent of the Smithwick Group IV patients (poorest prognosis) survived at a five year or longer follow up period Our limited experience with this small group of patients indicates that the Smithwick criteria seem to have some validity (From Am J Cardiol 2 227 1958 by permission)

case for the accelerated form of high blood pressure depending upon a qualitatively different mechanism [19] Pickering in 1955 [0] upheld the view point that the high diastolic blood pressure is the important variable just as Fishberg emphasized when writing in his 1940 edition [1] From their published reports I would judge that Page Pictte and Corcoran Schroeder [23] Smirk [4] Moyer [5] and Wolferth [6] are aligned with Pickering

II CLINICAL OBSERVATIONS OF THE AUTHOR

My own clinical experience suggests that there is no sharp line of distinction between advanced severe cases of primary hypertension and cases

of malignant hypertension" unless the presence or absence of papilledema is used as the criterion for their separation This criterion does not seem logical for we have seen patients with severe diastolic pressure who had an aggravation of their grade II hypertensive retinopathy with later appearance of exudate and retinal hemorrhages associated with further reduction in renal function as measured by the 15 minute phenolsulfonphthalein test (PSP) Fortunately further acceleration or the full blown malignant phase was slowed by more aggressive depressor drug therapy I conclude that patients might go into the "accelerated phase with only grade III Keith Wagener retinopathy changes if followed carefully and seen early in the "accelerated phase (Fig 1)

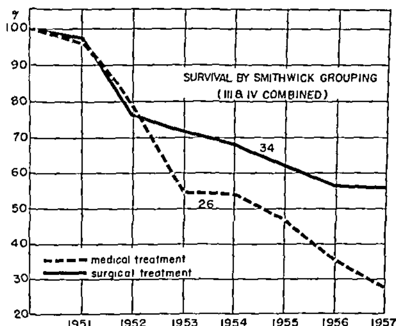


Fig 2 Fifty six per cent of the surgically treated patients whose vascular complications when first studied suggested that they should be grouped either as III or IV according to Smithwick survived Of the 26 medically treated patients only 28 per cent (7) have survived and only *one* patient survived who had bilateral papilledema at the time of his initial study in February 1952 (From Am J Cardiol 2 227 1958 by permission)

It is true that patients in the malignant phase are much more likely to exhibit evidence of advanced renal damage and in some little can be done to arrest the course of the disease I have followed through 1957 26 patients grouped in Smithwick group III and IV categories before 1951 Nineteen were azotemic at the time they were first seen and all are now dead[7] The survival curves for patients in Smithwick group III and IV medically treated appear to be the same This curve (groups III and IV combined) when compared with patients similarly grouped but surgically treated is less favorable (see Fig 2 and reference 27b)

I have not observed patients with malignant hypertension as earlier defined whose blood pressure had been satisfactorily moderated (since 1948 by means of surgery and since 1952 with depressor drugs alone plus surgery) developing more manifestations of hypertensive retinopathy as Perera

has reported[8] In summary on initial examination I find it difficult to know whether the patient has merely severe diastolic hypertension without severe renal damage or "malignant hypertension" with borderline azotemia The *important thing* is to reduce the pressure and if the renal dys function does not become worse at the lower renal artery *perfusion* pressure

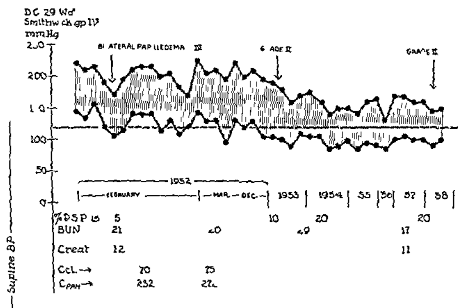


Fig 3 The blood *pressure response of the only patient now surviving* who had bilateral papilledema i e "accelerated phase at the time he was first seen in 1952 There appears to have been no aggravation of the impaired renal function then measured 5 per cent excretion of intravenous phenolsulfonphthalein (PSP) appearing after fifteen minutes blood urea nitrogen (BUN) 21 mg per cent and serum creatinine (Creat) 1 2 mg per cent with creatinine clearance (Ccl) 70 cc/min (normal 100 150) and estimated renal plasma flow (C_{PAH}) 232 cc/min (normal 400 1000) The elevated diastolic pressure has been moderated by a combination of hydralazine protoveratrine Rauwolfia extracts reserpine and since 23 October 1957 chlorothiazide D C had been troubled with severe frontal headache from February 1950 and was not found to have high blood pressure by his personal physician until August 1950 In August 1951 he was hospitalized in his home town because of diastolic pressures of 150 or higher hemorrhage in his right eye and was found to have nonprotein nitrogen 39 7 mg per cent 14 1 mg per cent urea nitrogen and fifteen minute PSP excretion 17 per cent one hour total 52 per cent two hour total 69 per cent Maximal specific gravity then (Mosenthal) was 1 016

This patient would then fit the major criteria of malignant hypertension Although surgical management was recommended this was not advocated vigorously in 1952 because of the patient's poor renal function The patient elected to have intensive depressor drug treatment and has been symptom free for six and one half years with no evidence of either progression of or improvement in the renal functional impairment

levels then the patient will live longer If not the patient will die of azotemia in months or years

III ACUTE PHYSIOLOGICAL EXPERIMENTS IN HYPERTENSIVE PATIENTS OF SMITHWICK GROUPS III AND IV

The cerebrovascular resistance was calculated from measurements of the mean arterial blood pressure and of the cerebral blood flow (nitrous

oxide method) and the eyegrounds were evaluated initially in 21 patients and then finally in 101 hypertensive patients [29, 30] A significant correlation was found between the grade of retinal hypertensive change and the cerebro vascular resistance The relationship was a direct one in that as cerebrovascular resistance increased the grade of retinopathy also tended to increase Smithwick group IV patients with papilledema were found to have the increased cerebral vascular resistance reduced *pari passu* when they were restudied, their blood pressure having been moderated in the interval by a surgical procedure [31] A recent attempt to determine the present status of patients so studied using the Kety Schmidt cerebral blood flow technique between 1946 to 1951 has disclosed that no one of these patients is now living who did not have a surgical procedure to moderate the high diastolic pressure [32]

The most important conclusion drawn from these studies is that the increased cerebrovascular resistance present in patients with severe diastolic hypertension having the malignant stage is not a fixed condition The reduction in blood pressure resulting from sympathectomy or subtotal adrenalectomy alone or combined with sympathectomy does not reduce cerebral blood flow

IV CURRENT EXPERIMENTAL ANIMAL STUDIES AS TO THE MECHANISM OF THE INCREASED PERIPHERAL VASCULAR RESISTANCE

Although in the twenty years since I have been interested in the mechanisms of high blood pressure much has been learned concerning hemo dynamics and its neurogenic and hormonal controls relevant to blood pressure levels there are still great gaps in our knowledge These voids are large enough to handicap attempts to formulate useful hypotheses concerning blood pressure regulation to say nothing of its derangements For the purposes of discussion we would like to emphasize Dr Goldblatt s credo that all essential hypertension is ultimately of renal ischemic origin [3] There is some basis in fact for implication of the kidney in the homeostasis of arterial pressure

The hemodynamics of hypertensin conform reasonably closely to the pattern of human hypertension and Skeggs makes an impressive case for an increase in this substance in human hypertensive blood in the accelerated phase when compared with subjects in the uncomplicated primary hyper tension disturbance and in normotensive subjects similarly studied [33]

However in the experimental animal we have not been impressed with this close conformity when synthetic hypertensin II received from Rittel and coworkers [34] is utilized in an infusion of one microgram per kilogram per minute This particular dosage leads to an increase in pulmonary arterial pressure and some reduction in cardiac output at a time when the blood pressure and left ventricular work are increased more markedly than by a comparable dose of either norepinephrine epinephrine or nicotine [3] Wakerlin has commented on similar observations as being "much more of an argument against the renin or hypertensin pathogenesis of experimental renal hypertension and of essential hypertension "[36] Our attempts to learn how the coronary blood flow and cardiac metabolic patterns when the blood pressure is acutely increased conform to the coronary blood flow

measurements made in the natural chronic experiment in man have not been fruitful as to a better understanding of how the heart muscle adjusts to the increased load of left ventricular work[37]

V SUMMARY

My thesis is that the severely elevated arterial pressure in patients with primary hypertension may be looked upon as reflecting an uncompensated impairment in hemodynamic coordination caused by abnormality of unknown origin of the neurogenic or hormonal control of part or parts of the circulatory apparatus The malignant or accelerated phase of the high blood pressure disturbance may be considered a speeding up of the destructive changes going on in the blood vessels particularly those of the kidney At the moment we do not know whether in the human this may lead to a liberation of or the uncoupling of the substance called hypertensin II which could be responsible for the very marked increase in the diastolic levels and thus lead to a complex of unknown factors resulting in further vascular disturbance and disease The fact that this accelerated or malignant phase may be seen in a variety of types of high blood pressure including that associated with chronic pyelonephritis chronic glomerulonephritis pheochromocytoma aldosteronism Cushing's syndrome polycystic and congenital small kidneys eclampsia nephrocalcinosis tuberculous pyelonephritis scleroderma polyarteritis disseminated lupus and coarctation of the aorta does not exclude the possibility that the same pathogenetic mechanism is at work in both the malignant and benign disease states[17]

The lesions found in the fundus oculi when the diastolic pressure is high might be considered as Schroeder has suggested a consequence of plethora or excessive hyperemia[3] If the artery supplying an area of the retina were diseased so that it could not contract and healthy" vessels in the remainder of the body were made to constrict hyperemia through that diseased vessel would result Excessive flow and pressure would be transmitted to the capillary bed supplied by that artery When venous outflow became insufficient to carry off the increased load water thin plasma and finally red blood cells would be forced through the capillary wall This idea explains what we see edema "cotton wool" exudates and hemorrhages tending to distinguish those patients in the "accelerated phase from the larger group with a less severe high blood pressure disturbance Frayer and Finnerty suggest another mechanism[18, 37] Our acute experiments indicated that there is a correlation of increased retinal vascular resistance with the increased cerebrovascular resistance and that this can be reduced *pari passu* as the high diastolic pressure is moderated

VI CONCLUSION

The important therapeutic conclusion is that blood pressure reduction *per se* seems to me to be reasonably well established as the one important factor in arresting vascular deterioration Other causes remain to be elucidated Methods for reducing blood pressure may be varied The important element is that they are effective Therefore surgical approaches ganglionic blocking agents centrally acting agents low salt intake rice diets oral nonmercurial diuretics and psychotherapy may all have beneficial effect as

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Causes of Death due to Hypertension The Effect of Therapy

JOHN R BEEM

Hahnemann Medical College and Hospital

Patients who die of hypertensive cardiovascular disease usually do so as a result of failure of cardiac renal or cerebral function Although multiple organs may be involved and several lethal mechanisms are frequently co active it is often possible to distinguish the one dominant organ failure Therefore the relative incidence of these three principal cardiovascular causes of death in primary hypertension may be considered Individual or biologic variation is characteristic of such phenomena consequently a study

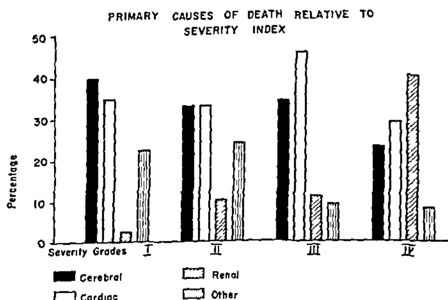


Fig 1 Primary causes of death relative to severity index Other refers to the per centage of patients dying of causes other than cardiovascular and to those whose outcome is unknown (Modified from R S Palmer and H Muench J A M A 153 1-4 1953)

of our data and published reports has been undertaken to ascertain some of the variables which influence these fatal hypertensive processes and to determine the effect of therapy thereupon

The height of the blood pressure and degree of retinopathy are known to be related to the severity of hypertension[1] As illustrated in Figure 1 they are also related to the incidence of the three principal cardiovascular causes of death In most mild cases (grade I) death is due to cerebral or cardiac complications In patients with hypertension which is exceptionally mild by all criteria the lethal cerebral and cardiac episodes are predomi

nantly the result of occlusive arterial disease Rarely in such patients is renal failure the principal cause of death In general these patients live for years and a considerable number ultimately die of causes unrelated to their cardiovascular disease In moderate (grade II) and severe (grade III) hypertension heart failure is the major cause of death Patients with accelerated hypertension (grade IV) usually die as a result of renal failure Congestive heart failure and cerebrovascular accidents are less frequently a principal cause of death One half or more of the cerebrovascular accidents are a result of hemorrhage [3]

Sustained elevation of diastolic blood pressure is thought to have a clinical significance differing from that of fluctuating hypertension The relative incidence of the three major types of cardiovascular death in non labile hypertension differs from that associated with labile hypertension [4] Patients with intermittent elevation of blood pressure usually die as a result of cardiac complications and only 16 per cent die of renal insufficiency (Fig 2)

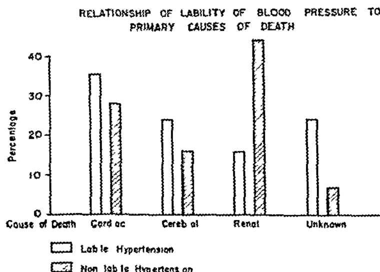


Fig 2 Relationship of lability of blood pressure to primary causes of death Forty four per cent of non labile patients and 16 per cent of labile patients had died at the time of the report (Modified from George A Perera J Chron Dis *1* 12 1955)

The role of occlusive arterial disease in patients with intermittent hypertension is indicated by the greater incidence (68 per cent) of coronary artery disease in this group * In contrast death due to sustained hypertension usually results from renal insufficiency and much less frequently from cerebral complications

Differences in the incidence of the major cardiovascular causes of death in hypertension may be related to age [5] The predominance of renal insufficiency in the early decades of life (especially in women) and the preponderance of cardiac and cerebral deaths in older age groups is illustrated in Figure 3.

* This appears to be even more significant inasmuch as 60 per cent of these patients were women, whereas in the non labile group only 32 per cent were women

Sex appears to have an influence upon the relative incidence of the principal cardiovascular causes of death in non accelerated hypertension The over all case fatality rate from hypertensive complications is almost 70 per cent greater in men than in women[6] Myocardial infarction[7 9] is much more frequent and cerebral hemorrhage[7 8 9] less common in men than in women Deaths due to heart failure[7 8 9] and renal insufficiency[5] are about equally divided between males and females

In relatively recent years it has become possible to reduce the blood pressure in many hypertensive individuals by surgical or medicinal therapy

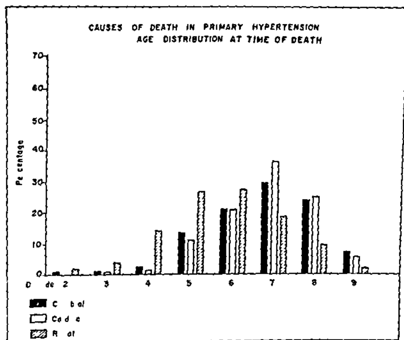


Fig 3 Causes of death in primary hypertension Age distribution by decades (Modified from E T Bell *Hypertension A Symposium* University of Minnesota Press Minneapolis 1951)

There are indications that a prolongation of life may result in patients who have severe[10] or accelerated disease[11 1] Although death may be delayed it ultimately results primarily from cardiovascular complications[12] In Figure 4 is illustrated the influence of modern antihypertensive therapy upon these causes of death in accelerated hypertension There is a marked reduction in the incidence of fatal renal insufficiency and congestive heart failure even though failure may have been present prior to therapy[13] As a result the three year survival is greatly increased The unprevented deaths resulting from renal insufficiency and cerebral hemorrhage often are associated with an inadequate reduction of blood pressure[1] Thrombosis in cerebral and coronary arteries is quite rare[14] Withdrawal of therapy is followed by an accelerated lethal course[13] These patients usually die within a very few months most frequently of renal insufficiency

The effect of modern antihypertensive therapy in non accelerated hyper

tension is illustrated in Figure 5 There is a striking reduction in the inci dence of fatal congestive heart failure and a slight diminution in fatal renal insufficiency[10, 15] A larger percentage of the cardiac deaths are a result of myocardial infarction[1, 1] however there is no increase in the absolute incidence of coronary thrombosis[15]

In considering the results of other therapeutic approaches to hyperten sion, similar trends are evident Surgical sympathectomy appears to de crease the number of deaths due to renal insufficiency and congestive failure[16, 17, 18] The relative incidence of cerebral and to a lesser degree myocardial infarction appears to rise slightly[16, 17] It is difficult to exclude

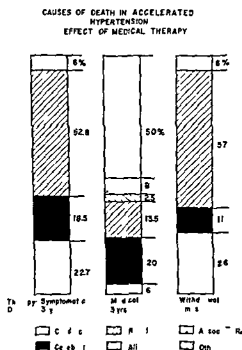


Fig 4

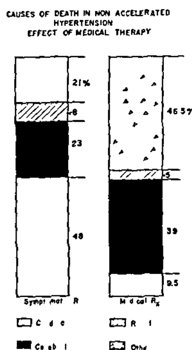


Fig 5

Fig 4 Causes of death in accelerated hypertension Effects of medical therapy From composite data[10, 1, 13, 24, 6, 7, 9]

Fig 5 Causes of death in non accelerated hypertension Effects of medical therapy From composite data[2, 7, 8, 10, 1, 16, 3, 4, 6, 0, 31, 8, 33, 34, 3, 36]

increased surgical selection as a possible interpretation of the lesser renal failure in sympathectomized patients however this would appear to be an unlikely explanation of the decreased congestive failure Available figures do not allow clear differentiation between sympathectomy of various extent as regards frequency pattern of cardiovascular deaths because other vari ables make minor differences difficult to interpret.

Similar directional changes in the cause of death occur after subtotal adrenalectomy combined with Adson sympathectomy although there is a suggestion that congestive failure may be even further reduced.[19] Total adrenalectomy without sympathectomy according to very limited data fails

to produce as marked alterations in relative causes of death as described for other therapeutic approaches [6, 1, 7]

Operative and other therapeutic deaths must be acknowledged but are not of prime importance to the current discussion Withdrawal of medical therapy already has been discussed in the light of resultant acceleration of renal lethal processes

The relative incidence of the three major cardiovascular causes of death in hypertension appears to form a variable pattern with one extreme being accelerated renal insufficiency the other being cerebral or coronary arterial occlusion Transitional patterns are marked by the high incidence of congestive heart failure In general the earlier in life the onset the higher and more sustained the elevation of blood pressure and the more pronounced the retinopathy the more likely is death to result from the rapid development of renal insufficiency or congestive heart failure These rapidly progressive lethal mechanisms in large part may be arrested or decelerated by reducing the blood pressure It is important to determine to what extent the slowly developing occlusive arterial factors (arteriosclerosis) are a result of or may be influenced by hypertension and to what extent these processes may be amenable to blood pressure reduction

Some patients may live twenty years or more after the first evidence of hypertension indicating a considerable individual variability in the course of the disease [23] Nevertheless such patients usually develop hypertension early in the fourth decade of life and die at the average age of 51 years many of them as a direct result of cardiovascular disease In contrast life expectancy from age 32 should approximate 73 years [5] About one third of the patients with exceptionally mild hypertension die after an average of 17 years largely of cardiac and cerebrovascular complications Therefore patients with so called "benign hypertension are not like old soldiers who merely fade away They die prematurely of cardiovascular insufficiency Obviously our major medical problem today is the prophylaxis against these slowly but progressive lethal processes

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The Effect of Blood Pressure Reduction on Prognosis in Hypertension

H MITCHELL PERRY JR
Washington University School of Medicine

THE PROBLEM

The problem is to quantitate the change in a hypertensive patient s prognosis after his blood pressure has been reduced In order even to ap proach this problem the prognosis in the untreated hypertensive patient must be known Theoretically the causes of death among untreated hyper tensive patients might be divided into three categories The first would include causes directly related to hypertension such as renal failure from arteriolar nephrosclerosis or cardiac failure from hypertensive cardiovascu lar disease The second would include causes indirectly related to hyper tension specifically causes like myocardial infarction and cerebrovascular *accident which are associated with atherosclerosis which in turn seems to* be associated with hypertension The third would include causes apparently unrelated to hypertension

It would be helpful to be able to group hypertensive patients according to the likelihood of their hypertension incapacitating them but even at autopsy it may be difficult to determine the contribution of each of several possible lethal factors Data like those of Smith Odel and Kernohan[1] at tempt to relate the severity of the hypertensive process to the cause of death These authors found that when hypertensive patients were divided into four groups on the basis of their fundal changes (Keith Wagener and Barker classification) from one half to one third of each group died of atherosclerosis *Almost two thirds of the patients with the least severe hy* pertension (group I) died of causes unrelated to their disease this fraction was successively halved for each of the three succeeding groups becoming negligible for the patients with the most severe hypertension (group IV) In contrast about two thirds of the patients with the most severe hyperten sion died of causes directly related to their disease with this fraction being successively halved for each succeeding group of less severely hypertensive patients

Both atherosclerosis and causes of death unrelated to hypertension are little affected by present antihypertensive therapy It is therefore reasonable to confine our attention to severely hypertensive patients who are liable to the sequelae of hypertension Even *with this limitation there is great diffi* culty in obtaining similar and homogeneous series of variously treated pa tients for comparison Criteria for grading the severity of hypertensive car diovascular disease differ greatly and such criteria are often partially subjective Moreover the populations so defined are somewhat heterogene

ous even at best Nonetheless when the severity of the hypertensive process has been the sole basis for selection of patients there has often been good agreement between authors Thus Keith Wagener and Barker found 5 4 months to be the median and 10 5 months to be the mean survival time after discovery of hypertensive papilledema while Palmer Loofbourow and Doering obtained a value of 4 0 months for the former[3] and Schottstaedt and Sokolow obtained a value of 8 4 months for the latter[4]

Despite apparently similar criteria of selection one series of hypertensive patients may differ markedly from another For example the pre sympathectomy renal function of Smithwick s patients with papilledema was demonstrably better than that of our non azotemic patients with malignant hypertension Nearly half of Smithwick s patients excreted at least 25 per cent of intravenously injected phenol red in 15 minutes[5] whereas none of our patients was able to do so[6] In addition the percentage of Negroes with their apparently poorer prognosis was presumably higher in St Louis than in Boston Such differences must be recognized when results are compared In addition to these differences and perhaps others which are not readily apparent most surgical series of severely hypertensive patients have been intentionally selected to avoid groups with high operative mortalities such as old subjects and subjects with renal or cardiac dysfunction In contrast many series of untreated and medically treated patients have been taken consecutively with no exclusions

The difficulties of comparing different authors series of patients naturally increase if the basis of selection is broadened to include the severity of the atherosclerotic as well as the hypertensive process as is done in Smithwick s and several other schemes of classification Both a resting diastolic pressure over 140 mm Hg and less hypertension coupled with cardiac failure or cerebrovascular accident are ominous but they suggest dissimilar outcomes and certainly need not imply the same life expectancy

THE DATA

The data can be divided into three general groups on the basis of whether the antihypertensive therapy involved surgery diet or drugs With each of the three kinds of treatment the results depended both on the details of the procedure and the selection of the patients Since time only permits brief mention of a few of the many clinical results I have selected several representative regimens for several categories of patients In order to concentrate on the most significant results only relatively severely hypertensive patients have been considered Uniform follow up periods were thought to be highly desirable and four years was chosen as approaching the maximum available for series of patients treated with antihypertensive drugs

Let us first consider surgery for malignant hypertension During the four years following thoracolumbar sympathectomy Smithwick observed a 48 per cent mortality among 114 non azotemic patients with malignant stages of hypertension characterized by papilledema in contrast the four year mortality of 37 similar patients who refused surgery was 98 per cent.[5] No detailed data are available relating postoperative diminution in blood pressure to period of survival for these patients

There is more information about patients with less severe hypertension

following the same surgical procedure These patients however were classified on the basis of both their hypertensive cardiovascular disease and their atherosclerotic cardiovascular disease (Smithwick classification) For 96 severely compromised patients (group IV) the mortality in the four years following surgery was 52 per cent and for 63 comparable untreated patients it was 87 per cent Similarly for 115 somewhat less severely compromised patients (group III) the four year mortality was 19 per cent and for 59 comparable untreated patients it was 58 per cent [7] Of 31 severely compromised patients (group IV) 7 for whom there was a reduction of at least 10 mm Hg in diastolic blood pressure to less than 110 mm Hg had a mortality of 14 per cent in the 5 to 11 years following surgery whereas the other 24 for whom there was no significant change in pressure had a mortality of 79 per cent during a somewhat shorter follow up period Similarly of 83 less severely compromised patients (group III) 27 with a fall in pressure had a 7 per cent mortality in comparison to the 30 per cent mortality for the 56 with no change in pressure [7]

Let us next consider less extensive surgery for malignant hypertension Peet and Isberg observed a 72 per cent mortality during the four years following thoracic rather than thoracolumbar sympathectomy for 130 patients with malignant hypertension characterized by rapid clinical course with constitutional involvement papilledema, and high diastolic pressure 13 azotemic patients all of whom quickly died were omitted from consideration [8] That Peet and Isberg reported a higher mortality than Smithwick might reflect a difference either in the efficacy of the surgical procedures or in the severity of the patients hypertension Although mortality is not given as a function of postoperative reduction in blood pressure it is stated that 4 patients were normotensive five years after surgery 12 remained hypertensive despite significantly reduced diastolic pressures, and 5 retained their preoperative hypertension

Let us now turn to salt restriction for malignant hypertension Newborg and Kempner do not specifically state the mortality among 156 patients with malignant hypertension characterized by papilledema after four years of rice fruit diet but their data define it as being between 60 and 83 per cent [9] Although their patients are probably comparable to the original untreated series reported by Keith Wagener and Barker [2] they are not comparable to the non azotemic surgical series considered above Newborg and Kempner included 37 patients with significant azotemia all but 3 of whom died within 12 months Between one half and one quarter of their patients with minimal or no nitrogen retention were alive after four years of therapy The average diastolic pressure of their 61 patients who survived a year of rice fruit diet fell to 109 mm Hg from a pretreatment level of 134 mm Hg but the relationship between survival and lowered blood pressure is not stated

Finally let us consider drug therapy for varyingly severe hypertension In considering the effects of antihypertensive drugs I have turned to our own series of patients because I have information relating blood pressure to prognosis All of these patients received a combination of ganglion blocking agent and hydralazine Presumably similar results would be observed with other equally effective drug regimens Our patients treated with drugs could be divided into three groups on the basis of whether their diastolic pressures were uncontrolled partly controlled or adequately controlled The first group consisted of patients who discontinued therapy during its first

year and promptly had a recrudescence of their pretreatment hypertension The second group consisted of patients who continued therapy under our direction for four years or until they died but whose average diastolic pressures in the sitting position were 100 mm Hg or higher The third group consisted of patients who also continued therapy and whose average diastolic pressures were below 100 mm Hg

Of 82 patients with malignant hypertension half survived four years of drug therapy [6] The criteria for malignant hypertension were papilledema hemorrhagic and/or exudative retinitis an average diastolic pressure over 120 mm Hg at hospital rest proteinuria and further evidence of renal dysfunction These patients were consecutively chosen with the only exclusions being 6 patients who during their initial visit were found to have more than 100 mg of non protein nitrogen per 100 ml of plasma As indicated in Table 1 14 of the 82 patients had uncontrolled diastolic pressures and all died within four years of beginning treatment for the 20 with partly controlled pressures the four year mortality was 60 per cent and for the 48 patients with adequately controlled pressures it was 31 per cent [6]

TABLE 1 FOUR YEAR MORTALITY IN PER CENT FOR VARIOUS GROUPS OF OUR DRUG TREATED PATIENTS AS A FUNCTION OF POST TREATMENT BLOOD PRESSURE

GROUP OF PATIENTS	NO OF PATIENTS	UNCONTROLLED DIASTOLIC PRESSURE	PARTLY CONTROLLED DIASTOLIC PRESSURE	ADEQUATELY CONTROLLED DIASTOLIC PRESSURE
All malignant hypertensives	82	100	60	31
Non azotemic Smithwick group IV	93	100	35	18
Smithwick group III	77	33	7	4

Among the 82 patients discussed in the last paragraph were 47 with no nitrogen retention This subgroup of non azotemic malignant hypertensive patients had a better prognosis than the azotemic patients with 36 per cent surviving four years of drug therapy Forty six additional patients without the stigmata of malignant hypertension were classified as belonging to Smithwick s group IV their four year mortality was 30 per cent These 93 non azotemic patients seemed to form a surprisingly homogeneous group As indicated in the table the mortalities for 13 uncontrolled 20 partly controlled and 60 adequately controlled patients were 100 35 and 18 per cent respectively [6]

Seventy seven less severely hypertensive patients classified as belonging to Smithwick s group III had an over all mortality of 10 per cent during the four years following inception of drug therapy As indicated in the table the mortalities for the 9 uncontrolled 11 partly controlled and 57 adequately controlled patients were 33 7 and 4 per cent respectively [6]

SUMMARY

Surgery diet and drugs can all prolong the lives of some severely hypertensive patients Following thoracolumbar sympathectomy in non azotemic

patients belonging to Smithwick s group IV about a quarter of the patients had reduced diastolic pressures After 5 or more years the patients with reduced pressures had a mortality of 14 per cent as compared to a mortality of 79 per cent for those with no change in pressure About two thirds of similar patients maintained average sitting diastolic pressures below 100 mm Hg following ganglionic blockade plus hydralazine with more than half of the remainder having some reduction in diastolic pressure on this regimen The mortalities for those with adequately controlled partly controlled and uncontrolled diastolic pressures were 18 35 and 100 per cent respectively

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Discussion

FRANCIS WOOD *Moderator*

JOHN BEEM	MARVIN MOSER
QUENTIN DEMING	JOHN H MOYER
WILLIAM DOCK	H MITCHELL PERRY JR
JOSEPH H HAFKENSCHIEL	HENRY SCHROEDER

DR. WOOD Dr Moser you believe that heredity and environment contribute to hypertension but you are not quite sure race has anything to do with it Is that right?

DR. MOSER No I believe that race may be more important than environment

DR WOOD Do you have statistics to prove it?

DR MOSER Not definitive ones

DR WOOD This is what we are up against Statistics are not adequate and further statistics must be collected concerning all phases of hypertension Dr Deming is hypertension related to atherosclerosis and if so how?

DR DEMING I think I d like to pick at the phraseology and say it should be the other way Atherosclerosis is intensified by hypertension We do not know how

DR WOOD Dr Hafkenschiel are malignant and benign hypertension the same or different diseases?

DR HAFKENSCHIEL I think that they are not different

DR WOOD Is malignant hypertension something that may or may not be grafted on benign hypertension?

DR HAFKENSCHIEL I think that malignant hypertension can occur in every benign hypertensive patient

DR WOOD Can it happen to anybody else?

DR HAFKENSCHIEL I dont know

DR MOYER I should like to support Dr Hafkenschiels conclusion with some case examples Figure 1 summarizes the renal deteriorating effects of a patient with malignant hypertension The course was no different from that observed in the patient in Figure 2 who had nonmalignant hyperten

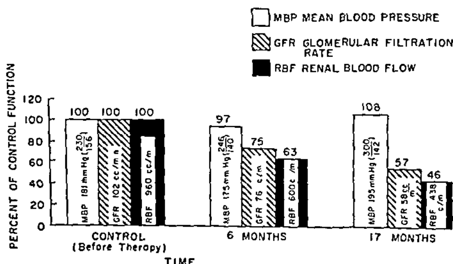


Fig 1 A patient with malignant hypertension who was not treated for a period of seventeen months There was progressive reduction in glomerular filtration rate and renal blood flow A few weeks after the last renal function test was performed the patient died of congestive heart failure and renal failure (From Am J Med *24* 177 1958)

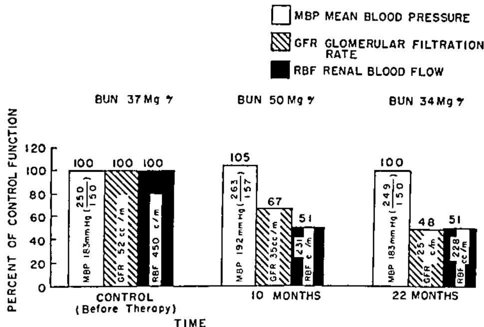


Fig 2 The effect of severe (nonmalignant) hypertension on renal function over a period of two years in a patient who was not treated with antihypertensive therapy Deterioration was progressive (From Am J Med *24* 177 1958)

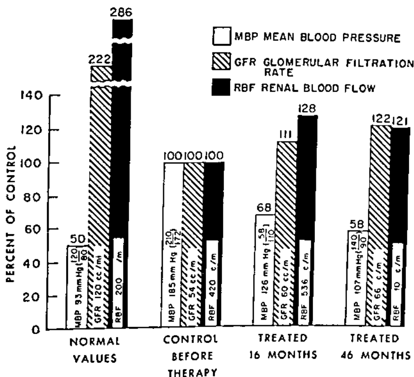


Fig 3 Summary of results in a patient with malignant hypertension who was treated effectively with antihypertensive agents (Rauwolfia plus ganglionic blockade) Prior to the institution of therapy the glomerular filtration rate and renal blood flow were depressed to less than 50 per cent of normal owing to the vascular deterioration associated with malignant hypertension However following effective antihypertensive therapy for a period of four years there was no further reduction in glomerular filtration rate and renal blood flow This indicates that the vascular deterioration associated with malignant hypertension can be arrested by effective antihypertensive therapy (From Am J Med *24* 177 1958)

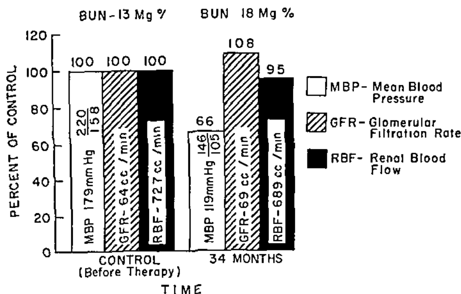


Fig 4 Renal effects of severe hypertension (nonmalignant) on renal function in a patient who was treated for a period of three years with antihypertensive therapy Note that there was no further deterioration of the renal vascular system as indicated by the glomerular filtration rate and renal blood flow following institution of antihypertensive therapy Compare this response with Figure 2 showing evidence of progressive vascular deterioration over a period of two years (From Am J Med *24* 177 1958)

sion Renal deterioration progressed very rapidly When two similar patients were treated adequately (Figs 3 and 4) renal vascular deterioration was arrested There was no difference in the effect of blood pressure reduction in the patient with malignant hypertension and the one with nonmalignant hypertension Retinal hemorrhages whether they be in a patient with malignant hypertension or nonmalignant hypertension respond in the same way to blood pressure reduction that is they clear up

Dr Wood In other words Dr Hafkenschiel thinks malignant hypertension is something grafted on benign hypertension Possibly it is an extension of a similar process The causes of death due to hypertension Dr Beem are in the heart the brain the kidneys and in automobiles is that right?

Dr Beem Yes Dr Wood

Dr Wood And therapy seems to be able to change these statistics?

Dr Beem That is true

Dr Wood And you have statistics which are moderately convincing?

Dr Beem We feel that the pattern of death certainly has changed As I said I think that it is premature to discuss definitely the changes of non accelerated hypertension

Dr Moyer Statistics which we collected in Houston support this concept

TABLE 1 CAUSES OF DEATH IN TREATED AND UNTREATED PATIENTS WITH HYPERTENSION

CAUSE	NUMBER (TOTAL)	TREATED*		UNTREATED†	
		NO	%	NO	%
Uremia	15	0	0	15	100
Cerebrovascular accident	19	9	47	10	53
Cardiac	4	0	0	4	100
Cerebrovascular accident with uremia	3	1	33	2	67
Others	3	1	33	2	67
Total	44	11	25	33	75
Average survival time (months)		22		11	

* Total number treated was 90
† Total number not treated was 43

From 1951 to 1954 we did differential renal function studies on a group of 133 patients most of whom had severe hypertension When we did follow up studies three or more years later 44 of these patients had died The causes of death are summarized in Table 1 Not any of the patients who were treated effectively died in uremia, whereas 15 of the untreated patients died of uremia

Dr Wood Dr Perry does blood pressure reduction improve prognosis?

Dr Perry Yes it does However I must place a question before you Is it possible that the patients whose blood pressures are not reduced by treatment could improve their prognosis by taking more drugs or is there something which confers on these patients more resistance to antihypertensive measures and condemns them to a poorer prognosis?

Dr Wood This is an important question A skeptic could contend that those who respond to hypertensive medication are the ones who are going to live a long time even if we don t treat them We have no controls to settle that problem Am I correct about that?

Dr Perry Not exactly I feel very strongly that in malignant hypertensives the mortality among untreated people is 98 or 99 per cent over a period of several years With any one of several methods of therapy this can be reduced to 50 per cent or less But is there something inherently different in the remaining 50 per cent that makes it difficult or impossible to lower blood pressure and thus improve the prognosis in these patients?

Dr Moyer Table 2 summarizes some observations that we have made

TABLE 2 SURVIVAL RATE IN PATIENTS WITH MALIGNANT HYPERTENSION

	NO PATIENTS	SURVIVAL 1 YEAR OR MORE	SURVIVAL 2 YEARS OR MORE
Untreated (nonuremic)	22	27%	9%
Treated			
Azotemia (nonuremic)	15	60%	60%
Normal BUN	11	91%	73%
Uremia	28	None	None

on treated and untreated patients with malignant hypertension There is little doubt that blood pressure reduction has improved the prognosis in patients with malignant hypertension

DR WOOD I was thinking about the nonmalignant type We do not know whether those patients who respond well would not have done as satisfactorily even if their blood pressures were not altered Is that correct?

DR HAFKENSCHIEL Dr Wood I have a specific reservation in relation to your comment I would like to know whether any panelists share this observation If one places some of these benign hypertensives on placebo therapy there appears to be an unusually high incidence of cerebrovascular accidents This implies that benign hypertensives require effective therapy also and that blood pressure reduction improves the prognosis

DR SCHROEDER I agree with Dr Hafkenschiel there is no doubt that treatment improves the prognosis

DR WOOD I agree with Dr Hafkenschiel and Dr Schroeder but definitive statistics are not yet available concerning the results of treatment in benign hypertension There is no doubt in my mind that these people will show an improved life expectancy and that cerebrovascular accidents and heart failure are decreased in these people by treatment

DR DOCK Dr Hafkenschiel mentioned coarctation of the aorta as one of the forms of hypertension that developed malignant change Do you know any patients with coarctation who died of uremia with the changes in the renal arterioles that we observe in malignant hypertension?

DR HAFKENSCHIEL I do not have any such patient in my own series However I believe an unpublished observation of Goodwin is mentioned in a paper by Kincaid Smith McMichael and Murphy

DR WOOD Is there only one such case?

DR HAFKENSCHIEL I had a young patient with coarctation who had bilateral papilledema which in a sense is a phase of malignant hypertension as I defined it in my paper

DR DOCK This concerns the basic question of whether hypertension does harm to blood vessels We admit it does harm to the vessels above a coarctation but when you contend that in coarctation the renal arterioles are affected it is disturbing

DR HAFKENSCHIEL I think that is a good point I have not seen any renal biopsy specimens

DR DEMING I think that Dr Hafkenschiel should not concede so readily The definition of malignant hypertension does not include necessarily changes in the kidney Clinically malignant hypertension is based either on the level of the blood pressure or the appearance of the eye grounds Pathologically it is based on the status of the arterioles which must be necrotizing These do not have to be in the kidney They can be in the brain or anywhere else

DR DOCK Once they occur below the diaphragm in coarctation all the theories about the blood pressure producing vascular changes in malignant hypertension come into doubt If this was proven in any one case it would imply that the changes are due to a humoral effect and not to a pressure load Apparently this has not been observed

DR MOYER I would just like to ask Dr Deming if he has any ideas as to the origin of the increased arterial oxygen uptake and metabolism in hypertension and why this would be reversed by blood pressure reduction

DR DEMING Are you referring to the increased oxygen uptake of the vessels?

DR MOYER Yes

DR DEMING These studies were in rats I think we can offer only two possibilities Since there is obvious medial hypertrophy and an increase in muscle mass this should cause some increase in the total oxygen uptake In addition apparently there is increased metabolic activity of that increased muscle mass Why it is more active when it is isolated and no longer under the stress of the blood pressure elevation I do not know It does raise the possibility that changes are taking place which may affect other types of metabolism as well

DR MOYER Do you think this could be enzymatic in origin?

DR DEMING There was a change in one enzyme which was measured

DR MOYER Do you have any ideas as to why sympathetic depressive drugs which reduce blood pressure also lower blood cholesterol?

DR DEMING *I assume that the cholesterol comes down when the blood* pressure is lowered for the reciprocal of the reason that it goes up when the blood pressure goes up

DR. WOOD I would like to make one observation We do not yet know why all people with elevated blood pressure do not die This raises the question of who is to be treated and why Right now every one of us very enthusiastically is treating many people Ten years from now we will know whether these patients are better off than if they had not been treated

Observations on Cardiac Output, Peripheral Blood Flow and Blood Volume in Hypertension—Before and During Treatment

EDWARD D FREIS

Georgetown University School of Medicine

There is general agreement among investigators that the total blood volume and cardiac output are normal in uncomplicated hypertension The cardiac output is maintained in the normal range however by an increase in the residual volume of the left ventricle which comes about as follows If aortic pressure is suddenly elevated from the normal to the hypertensive range the stroke volume of the left ventricle diminishes owing to the increased resistance to outflow The retained blood increasing from beat to beat distends the ventricular chamber and stretches the myocardial fibers Since according to Starling s law the force of contraction is proportional to the diastolic fiber length the strength of ventricular contraction increases from beat to beat until a point is soon reached at which output is restored but at the expense of an increased residual volume in the left ventricle Also since the heart now is performing more work than it had previously hypertrophy of the muscle fibers gradually occurs

This process of compensation has its limitations beyond which further increases in diastolic fiber length result in progressively diminishing rather than increasing cardiac output The point at which failure occurs varies from heart to heart depending on other factors such as patency of the coronary circulation other disease states affecting the myocardium metabolic abnormalities and so on

When the heart fails in hypertension the symptoms often are those of pure left ventricular failure but decompensation may begin with signs of right ventricular failure The reasons for this appear to be various First the myocardium is a syncytium involving both ventricles When the contraction of the stronger or left ventricle is weakened it compromises to some extent the contraction of the right Second failure of cardiac output and reduction of aortic and carotid sinus pressures stimulate reflex sympathetic vasoconstriction including venoconstriction which shunts blood into the central veins and right heart Third reduction in the velocity and momentum of the blood tends to displace a greater proportion of the blood volume to the venous side Fourth the fall in cardiac output through unknown pathways stimulates aldosterone secretion and renal conservation of salt and water This leads to an increase in total extracellular (including plasma) volume and further aggravates venous congestion

Peripheral blood flow appears to be normal in hypertension and the pe

ripheral resistance seems to be more or less uniformly increased throughout the body Renal blood flow, however, often is decreased moderately

EFFECTS OF GANGLIONIC BLOCKING AGENTS

When a ganglionic blocking agent such as hexamethonium is injected intravenously into a patient with essential hypertension not complicated by congestive heart failure there is a decrease in mean arterial pressure and cardiac output without change in the total peripheral resistance Central venous and right heart pressures fall, indicating a reduction in venous return [1] This reaction can be studied in more detail in the dog by substituting a constant output pump for the left ventricle leaving the right ventricle undisturbed [2] Blood is drained from the left auricle into a reservoir from which it is pumped into the aorta through a T tube The right ventricle is not by passed in this preparation only the left ventricle being substituted for by the pump

When hexamethonium is injected into such a preparation there is at first a decrease in systemic arterial pressure indicating arteriolar relaxation since the left pump output is maintained at a constant rate Within one minute this is followed by a reduction in right ventricular output and pulmonary arterial pressure During the succeeding few minutes the reservoir level falls as several hundred ml of blood are transferred from the reservoir to the animal s vascular system Obviously the vascular volume or capacity of the dog had *increased* following hexamethonium and to an extent that could be explained only by assuming capillary and venular as well as arteriolar dilatation As a corollary to this it can be shown that sympathetic stimulation as exemplified by norepinephrine produces exactly opposite effects indicating a decrease in peripheral vascular volume Many other investigators have brought forth evidence to show the relationship between the sympathetic nervous system and the peripheral vascular system including venous tone right heart filling pressure and cardiac output [3,4]

In hypertensive patients with congestive heart failure the cardiac output increases after the administration of hexamethonium rather than decreases and the total peripheral resistance declines [1] Pulmonary right heart and central venous pressures also fall toward normal Dual effects operate in this case to produce the improvement First the decrease in aortic pressure reduces the work demand and permits greater left ventricular emptying The overstretched left ventricular diastolic fiber length is reduced to a point where the myocardium can contract more effectively Second the increase in peripheral vascular capacity drains blood away from the congested central veins permitting reduction in the overdistention of the right ventricle

Release of sympathetic tone using ganglion blocking drugs does not result in an even distribution of blood flow to the various regions of the body Foot and hand blood flow increase many fold particularly if their vasculature is under increased tone as occurs during exposure to cold environmental temperatures Muscle blood flow increases whereas splanchnic (hepatic portal) blood flow declines Renal blood flow decreases temporarily but in the absence of severe renal damage the blood flow soon is restored owing to the marked autonomy of the renal vasculature These data do not indicate that the sympathetic nervous system is of great importance in regulating arteriolar tone in the resting supine subject except for its role

in temperature regulation of the skin of the distal extremities The results also emphasize the fallacies inherent in drawing conclusions as to the over all vasodilating effects of agents which increase skin temperature color or blood flow

The sympathetic nervous system is undoubtedly of great importance in adjusting cardiac output arterial pressure and central venous pressure When the cardiac output and arterial pressure fall owing to blood loss or blood volume shifts such as occur on assuming the erect position the baro receptor reflexes initiate sympathetic reflex vasoconstriction This not only initiates arteriolar constriction but also reduces peripheral vascular capacity and shunts blood into the central circulation Following sympathetic inhibi tion with hexamethonium the arterial pressure becomes a direct function of the blood volume [7] If the blood volume is reduced by venesection in the supine hexamethonium treated subject a perceptible step wise fall of arterial pressure occurs with each 50 cc removed and as this is reinfused the pressure rises step wise back to the prephlebotomy level

SALURETIC AGENTS

The effect of saluretic agents or salt depleting diets on the cardiac output and arterial pressure is similar in some ways to the action of the ganglionic blocking agents However the effect is produced through an entirely differ ent mechanism which will be considered in more detail in the section on pharmacology In this section it is sufficient to make the following compari sons both the ganglion blocking drugs and the saluretic agents appear to lower blood pressure by reducing right heart filling pressure and cardiac output Ganglionic blockers accomplish this by increasing peripheral vascu lar volume in relation to an unchanged total blood volume Saluretic agents and salt depleting diets function by reducing total blood specifically plasma volume in the presence of an apparently unchanged or insufficiently re duced vascular volume or capacity Reduction in tissue pressure also may be a contributing factor

HYDRALAZINE

The effects of hydralazine or Apresoline on cardiovascular hemody namics are entirely different from those already described This drug pro duces changes which mimic those seen in fever It should be recalled that the hemodynamic effects of pyrogens still occur even after the febrile re sponse is blocked with antipyretics [7]

After hydralazine the cardiac output approximately doubles Since mean arterial pressure falls the total peripheral vascular resistance declines more profoundly than is the case with any other antihypertensive drug Because of this the decrease in diastolic pressure is prominent Because of the in creased stroke volume however systolic pressure is less affected

Hydralazine produces a characteristic redistribution of blood flows to various areas Blood flow is diverted primarily to the hepatic portal and renal areas which exhibit significant increases [8, 9] Teleologically this would be of obvious importance to an organism attempting to combat a pyrogenic infection Blood flow through the muscles of the extremities usually de creases slightly while digital or skin blood flow shows no significant change [9] Coronary blood flow increases [10]

THE VERATRUM ALKALOIDS

Following Veratrum viride the cardiac output does not change significantly unless the patient has congestive heart failure in which event it increases [11] When the pulmonary arterial pressure is normal it does not change but when it is elevated as in congestive heart failure it falls toward normal as the cardiac output increases Total peripheral resistance is reduced in all cases

The bradycardia but not the hypotension is vagal in origin and can be blocked with atropine Homeostatic vasoconstrictor reflexes ordinarily are not blocked by Veratrum Blood flow through muscular renal and hepatic portal areas shows no essential change although there may be initial decreases

As can be seen from these studies clinical effectiveness is not necessarily associated with complete reversal of the hypertensive process Thus of all the antihypertensive agents studied Veratrum produces the most physiologic hemodynamic reversal of hypertension On the other hand more effective drugs clinically such as chlorothiazide and the ganglion blocking drugs decrease cardiac output and produce other hemodynamic abnormalities It would appear that rather marked hemodynamic aberrations can be tolerated with benefit to the patient provided they reduce his blood pressure

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Cerebrovascular Changes and Cerebral Metabolism in Hypertension

PAUL NOVACK

Hahnemann Medical College and Hospital

Ten years have passed since the nitrous oxide method of Kety and Schmidt[1] became a standard method for the study of the human cerebral circulation and metabolism. *Hypertension was one of the first clinical entities to be investigated by this method,* and the hypertensive patient has continued to be of great interest to those concerned with cerebral hemodynamics and metabolism. It is the purpose of this paper to review briefly the results of such studies as they pertain to delineating the etiology of hypertension, explaining the clinical manifestations of hypertension, and evaluating the therapy of hypertension.

The possibility that some disorder of cerebral function lies at the basis of human essential hypertension has long been considered attractive but still remains difficult of proof. It was early evident that the patient with essential hypertension presents no abnormalities of cerebral blood flow or oxygen utilization as measured by the nitrous oxide method. Indeed, as is demonstrated in Table 1, there has been singular agreement in the results reported by various investigators.[3,4] The cerebral blood flow remains at the normal level of 53 cc./100 gm./min., and cerebral oxygen consumption remains at the normal value of 3.4 cc./100 gm./min. In the more detailed analysis of Hafkenschiel[4] such parameters as cerebral respiratory quotient and arterial and internal jugular venous oxygen content, carbon dioxide content, pH and pCO_2 were also normal. Furthermore, the degree of hyper*tension, sex and age seemed of little importance to the results obtained.* The lone abnormality thus far found is an increase of the cerebral vascular re-

TABLE 1. CEREBRAL BLOOD FLOW AND METABOLISM IN ESSENTIAL HYPERTENSION

REFERENCE	NO.	AGE	CBF (cc./100 gm./min.)	CMRO (cc./100 gm./min.)	CVR (mm. Hg/cc./100 gm./min.)	MABP (mm. Hg)
4	101	41	57	3.5	2.8	153
3	6	44	52	3.1	2.6	136
5	8	42	57	3.4	2.7	152
(Normals 3)	12	30	53	3.4	1.8	103

CBF: Cerebral blood flow.
CMRO: Cerebral oxygen utilization = CBF × Arteriovenous oxygen diff. across brain.

CVR: Cerebral vascular resistance $= \dfrac{\text{MABP} - \text{JVP}}{\text{CBF}}$

MABP: Mean arterial blood pressure.
JVP: Jugular venous pressure.

sistance and this is interpreted as being part of the generalized increase in arteriolar tone characteristic of essential hypertension

A brief consideration of the inherent limitations in the available method for the *in vivo* study of the human cerebral circulation and metabolism makes it evident however that these data provide no real basis for evaluating the possibility of a cerebral origin of hypertension The greatest handicap may be attributed to the high degree with which various cerebral functions are localized to discrete anatomic areas It is not presently possible to detect regional abnormalities of cerebral blood flow or metabolism only the grossest abnormalities of blood flow and metabolism of the brain as a whole are subject to detection It should further be emphasized that abnormalities in the intermediate stages of cerebral metabolism are not excluded by the finding of a normal oxygen utilization This sphere of study remains largely unexplored

Of the various cerebral manifestations associated with an elevated blood pressure hypertensive headache hypertensive encephalopathy and cerebral hemorrhage stand out Unfortunately the newer methods of physiologic study have added nothing to our understanding of the most calamitous of these events cerebral hemorrhage Our current views concerning cerebral vascular physiology of hypertensive headache and encephalopathy stem mainly from the observations of Moyer and associates [6, 7] The basic measurements of cerebral blood flow oxygen consumption vascular resistance and jugular venous pressure in patients with hypertensive headaches did not differ from similar measurements of these parameters in hypertensives without headaches The cerebrospinal fluid pressures in these cases were not remarkable Relief of symptoms was obtained by intravenous administration of aminophylline or caffeine each of which resulted in an increase in cerebral vascular resistance a decrease in cerebral blood flow and no change in arterial pressure [6] Some of these patients were considered to have hypertensive encephalopathy and the results were essentially the same

In another series [7] it was found that encephalopathy could be relieved by reducing arterial blood pressure with an intravenous Veratrum preparation In these cases cerebral blood flow was unaltered and cerebral vascular resistance was diminished. In an effort to explain similar clinical responses achieved by divergent effects upon cerebral hemodynamics the authors proposed that the occurrence of headache in hypertensive individuals is dependent upon the relationship between the height of the arterial blood pressure and the "tone of the cerebral vessels Thus hypertensive headache is attributed to a high blood pressure with a diminished tone resulting in distention of the intracerebral vessels hence the relief afforded by increasing the vascular tone with aminophylline or decreasing the blood pressure with Veratrum It was further postulated that hypertensive encephalopathy was a result of a more advanced phase of this same process In this instance it was postulated that the diminished arteriolar tone allowed for transmission of an increased pressure to the cerebral capillary bed leading to increased transudation of fluid from the vascular compartment to cerebral tissue resulting in cerebral edema Although these explanations of the observed facts seem reasonable one should not consider the issue closed

Without implying an etiologic relationship one may safely state that arteriosclerosis occurs in patients with hypertension and the term "hypertensive arteriosclerotic vascular disease" is customarily used to indicate the

TABLE 2 CEREBRAL BLOOD FLOW AND METABOLISM IN HYPERTENSIVE ARTERIOSCLEROTIC VASCULAR DISEASE

REFERENCE	NO	AGE	CBF (cc /100 gm / min)	CMRO$_2$ (cc /100 gm / min)	CVR (mm Hg/cc / 100 gm /min)	MABP (mm Hg)
5	15	44	42	2 5	3 4	138
3	14	58	38	2 5	3 6	135
5	65	67	41	2 3	3 6	140

combination Generally the term is used loosely with little attempt to distinguish between those afflicted with predominantly atherosclerotic lesions and those in whom arteriolarsclerosis prevails In any event as indicated in Table 2 the cerebral blood flow and the oxygen consumption in such individuals are not normal Both are reduced Furthermore the cerebral vascular resistance is higher than in the uncomplicated hypertensive This presumably reflects the additive effects of organic and vasospastic obstruction As pointed out by Fazekas [5] the depression of cerebral blood flow and oxygen consumption is of a similar extent in normotensive patients with cerebral arteriosclerosis although the occurrence of hypertension seems to predispose to the development of such changes at an earlier age The significance of the reduced oxygen consumption is difficult to interpret It may be a cause of a result of or independent of the reduced blood flow There is no general agreement on this point and arguments may be mustered to support each of these views

One of the first questions raised when effective hypotensive therapy became available concerned the possible harmful effects on the cerebral circulation The data accumulated over the past ten years have been sufficiently comparable to permit a general description of the response of the cerebral circulation to a reduction in blood pressure produced by surgery (Table 3) or drugs (Table 4) As arterial pressure is reduced cerebral vasodilatation occurs and the cerebral blood flow and oxygen consumption are maintained When the drop in blood pressure exceeds the ability for further vasodilatation cerebral blood flow falls but oxygen consumption tends to be maintained by virtue of more complete extraction of oxygen per unit of blood provided The pathway or mechanism by which such cerebral vasodilatation is accomplished in response to the diverse procedures listed has not been defined In spite of this homeostatic mechanism the therapy of the hypertensive arteriosclerotic individual must be approached with some cau

TABLE 3 CEREBRAL BLOOD FLOW AND METABOLISM FOLLOWING SURGICAL TREATMENT OF HYPERTENSION

REFERENCE	NO	CBF (cc /100 gm / min) I	II	CMRO$_2$ (cc /100 gm / min) I	II	CVR (mm Hg/cc / 100 gm /min) I	II	MABP (mm Hg) I	II
Lumbar Sympathectomy[8]	9	55	57	3.5	3 5	2 8	2 3	151	131
Adrenalectomy[9]	11	52	59	3 3	3 2	3 1	2 6	155	115

I Preoperative observations
II Postoperative observations

TABLE 4 CEREBRAL BLOOD FLOW AND METABOLISM IN HYPERTENSIVE PATIENTS FOLLOWING AN ACUTE REDUCTION IN BLOOD PRESSURE

		CBF (cc /100 gm / (min)		CMRO2 (cc /100 gm / min)		CVR (mm Hg/cc / 100 gm /min)		MABP (mm Hg)	
REFERENCE	NO	I	II	I	II	I	II	I	II
Differential spinal sympathetic block[10]	16	52	46	3 3	3 2	3 1	2 6	155	115
Arfonad[11]	12	49	48	2 7	2 7	3 2	2 0	147	84
Hydrazinoph thalazine[1]	8	56	57	3 6	3 2	2 8	2 1	144	113
Hexamethonium[13 14]	13	55	46	3 6	3 5	3 5	2 5	181	111
	7	60	35	3 5	3 1	3 0	2 5	179	89
Tetraethyl ammonium chloride[15]	10	39	33	2.3	2 4	3 8	2 8	133	77

tion Although such patients were shown by Bessman[1] to maintain cerebral blood flow and oxygen consumption in response to hypotension induced by tetraethylammonium chloride (Table 4) most nevertheless exhibited symptoms of cerebral ischemia It was felt that blood flow was probably not being equally well maintained in all areas of the brain and this situation was not reflected by the measurement of total cerebral blood flow

No discussion of the cerebral circulation is complete without reference to the unique effects of inhalation of carbon dioxide This agent produces selective cerebral vasodilatation even in patients with essential hypertension or hypertensive arteriosclerotic vascular disease[16 17] This effect is achieved without reduction in blood pressure hence cerebral blood flow is increased The reduction in cerebral vascular resistance so produced is as great as reported with any of the hypotensive procedures Although the inhalation of 5 per cent CO presents no apparent usefulness in the therapy of hypertension per se it has been suggested that this measure offers a convenient and safe means of assessing the respective contributions of vasospasm and organic obstruction to the production of an increased cerebral vascular resistance[16 18] Certainly the investigative potentialities of CO_2 have not as yet been exhausted

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Myocardial Metabolism in Hypertension

WILLIAM LIKOFF

Hahnemann Medical College and Hospital

The heart is an energy producing and utilizing structure with the precise function of supplying blood to the entire living being Myocardial metabolism refers to the sum of the chemical changes which occur within the muscle mass of this unique organ The details of these events in health and

disease have been as yet incompletely recorded Most of the past data have been obtained from studies on tissue slices and from the isolated perfused heart More recently the technique of coronary sinus intubation has provided information about metabolic processes with the heart in its usual environment [1] The present discussion includes myocardial metabolism in the normal heart the classification of disturbances in myocardial metabolism and the specific alterations observed in the various devolutionary stages of hypertension

METABOLISMS OF THE NORMAL HEART

The essential phases of cardiac metabolism are energy production and energy liberation

1 Energy Production The elements in energy production are food stuffs which serve as oxidizable substrates and the oxidative enzyme systems Otherwise expressed energy production involves the oxidation of carbohydrates proteins and fats to carbon dioxide through a large series of intermediary reactions

A *Carbohydrate Metabolism* The human heart utilizes glucose lactate and pyruvate [3] The extraction and usage of these substances are functions of their coronary artery blood concentration [4] Until certain upper arterial blood values are exceeded the extraction increases as the concentration rises

At normal levels glucose and lactate are used in approximately equal quantities However the total aerobic metabolism of glucose lactate and pyruvate accounts for only 35 per cent of the total myocardial oxygen consumption This obviously implies that the heart also utilizes non carbohydrate substances as sources of energy

B *Metabolism of Fatty Acids Amino Acids and Ketones* Catheterization studies indicate that the heart utilizes considerable quantities of fatty acids amino acids and ketone bodies [5] In the post absorptive state the contribution of these non carbohydrate materials to the oxidative metabolism of the heart doubles that of the carbohydrates Furthermore the exceptional contribution of fatty acids to the oxygen usage of the heart which takes place after a high fat diet suggests that fat itself actually is stored in the heart muscle [6] Although the precise role that lipids play in myocardial metabolism is obscure various pertinent explanations have been offered [8,9] These propose that the unesterified fatty acids are utilized by the myocardial cell as a source of energy production that the transport mechanism and usage of these substances is under hormonal control and that phospholipids may be concerned in maintaining contractility

The utilization of ketones is directly proportional to their arterial concentration and inversely proportional to the quantity of available carbohydrate

Although the human heart is capable of extracting large quantities of amino acids from the coronary blood this does not imply they are stored Amino acids may form glycogen or nitrogenous compounds or may be oxidized to some members of the citric acid cycle

The avidity of the heart for and its versatility in utilizing carbohydrates and non carbohydrates may be viewed as an important factor of safety It is likely that the utilization of these materials is regulated entirely by their relative availability and the functional capacity of specific enzyme systems

2 ENERGY LIBERATION The essential elements in energy liberation are the proteins actin and myosin their conjugate actomyosin the energy carrier adenosine triphosphate (ATP) potassium phosphocreatine and the various enzyme systems

In the resting muscle the dissociated proteins actin and myosin are kept apart by the intracellular potassium ions With depolarization the cell membrane becomes permeable to potassium The resultant reduction in the intracellular concentration of this ion permits the union of the proteins and the formation of the contractile protein actomyosin to which adenosine triphosphate is promptly absorbed Immediately following such action a high energy phosphate band is split off thus supplying the actomyosin fiber with energy for contraction

During repolarization potassium reenters the cell Adenosine triphosphate is regenerated from the residual diphosphate and its high energy phosphate bond is restored The phosphorus is obtained in the enzymatic oxidation of carbohydrates or from stores of phosphocreatine Actomyosin now is separated from the adenosine triphosphate and actin from myosin because of the increase in the concentration of intracellular potassium and the restoration of ionic equilibrium

METABOLISM OF THE HEART IN HYPERTENSION

Theoretically disturbances in myocardial metabolism are divided into those of energy production and of energy utilization and liberation The intricacies of the problem however and the limitations of present investigative techniques are such that the finite phases of metabolism cannot always be separated easily To complete the issue these disturbances may or may not be accompanied by an alteration in the mechanical efficiency of the heart

Arterial hypertension represents a chronic pressure load upon the myocardium Because of the increased peripheral resistance the intraventricular pressure must be elevated abnormally so that blood can be ejected into the arterial circulation In order to effect greater contractile force the myocardial fibers respond by increasing their diameter Thus muscular hypertrophy assumes the role of a natural and effective compensation

For the present no information is available as to the specific metabolic alterations which exist with this initial phase of this response When the ventricular walls thicken appreciably the myocardial fibers probably suffer a diminution in distensibility thereby requiring a greater filling pressure to attain a particular diastolic volume The diameter of the hypertrophied myocardial fiber may increase to twice the normal size Under the circumstances a relative insufficiency of blood supply develops because of the increased diffusion distance between the capillaries and the cell The devolutionary pattern of events therefore that is initiated by myocardial hypertrophy ultimately leads to the loss of mechanical efficiency and the development of congestive failure The same end results namely insufficient arterial blood supply and heart failure may arise directly because independent occlusive coronary atherosclerosis is common in the presence of hypertension

The exact nature of the metabolic disturbances at many points in this sequence of events is unknown However studies have been carried out in

two areas that of congestive heart failure and myocardial infarction In vestigation in human subjects with congestive heart failure has revealed no serious alterations in energy production The oxidation of carbohydrates and non carbohydrates continues normally and there is no evidence of anaerobic metabolism [10] Accordingly the metabolic fault leading to mechanical in efficiency must reside in energy liberation and utilization However it is unknown whether the difficulty exists in the production or release of the high energy phosphorus bond or within the contractile proteins of the heart

Following experimental occlusion of the coronary circulation the con centration of pyruvate and lactate increases in the coronary venous blood suggesting an impairment in oxidation Myocardial usage of glucose con tinues unabated probably as the result of anaerobic glycolysis [11] These metabolic changes quickly reversible are followed by increases in the peak activity of specific enzymes Thus far however coronary sinus catheteriza tion has failed to reveal more definitive alterations in the metabolic patterns of energy production or energy utilization

It is quite apparent that only limited information is available concerning *the gross and subtle changes in the metabolism of the hypertensive heart* This is particularly true of the earliest phases of the disease process Even the alterations noted under the circumstances of congestive failure and myocardial infarction are only an incomplete explanation for the severe abnormality which develops in mechanical inefficiency

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Renal Hemodynamic Changes in Patients with Hypertension

JOHN H MOYER
Hahnemann Medical College and Hospital

The frequent coexistence of renal disease and hypertension is well known and the relationship between the kidney and hypertension has been the basis for much experimental and clinical investigation Irrefutable evidence is accumulating which indicates that severe hypertension produces renal damage and that the degree of renal damage is proportional to the severity of the hypertension It is also probable that the blood pressure elevation precedes the renal damage in essential hypertension With adequate blood pressure control the renal vascular changes associated with hypertension can be arrested but usually cannot be returned to normal

We have studied a group of hypertensive patients in whom the renal functional status was determined by means of renal clearance techniques i e glomerular filtration rate and renal plasma flow The data have been analyzed in an attempt to establish the correlation if any between the incidence and severity of depressed renal function and the degree of blood pressure elevation In addition a comparison has been made between the incidence and severity of renal functional alterations and complications of hypertension in other vascular beds such as the brain and heart using ordinary clinical observations for evaluating the latter changes

It is difficult to express in numerical terms the functional capacity of vital vascular beds other than the kidney Since this can be done for the kidney and since the blood vessels in the kidney are so responsive to blood pressure elevations the current renal hemodynamic studies can be used as an index of the vascular changes that occur elsewhere in the body

METHODS

This study consisted of a group of 133 patients* with hypertension picked at random from a city county hypertension clinic All of the patients had a sustained elevation of the blood pressure above 150/100 mm Hg in both the supine and upright positions during an initial control observation period of three to four weeks while receiving placebo therapy only Patients with evidence of primary renal disease and patients with obvious clinical manifestations (excluding laboratory studies) of uremia were excluded from the study irrespective of the cause of renal failure

On the initial visit to the clinic a complete history was obtained and a physical examination was performed In addition certain laboratory examinations were obtained including a complete blood count urinalysis blood urea nitrogen electrocardiogram and a roentgenogram of the chest Each patient was started on placebo medication and blood pressure determina

*Material obtained from report by Moyer et al Am J Med 24 177 1958

tions were made with the patients in both supine and upright positions once or twice a week for a period of three to four weeks Renal function studies were performed during this observation period and consisted of determinations of the glomerular filtration rate by the inulin clearance method and renal plasma flow by the clearance of para aminohippuric acid The renal blood flow was calculated from the renal plasma flow The technique and analytical procedures of the clearance tests have been described previously[1 2 3]

OBSERVATIONS

Table 1 summarizes the vital statistics and complications of hypertension

TABLE 1 VITAL STATISTICS AND COMPLICATIONS IN HYPERTENSIVE PATIENTS

DATA	VALUES	COMPLICATIONS	NO OF PATIENTS	%
Total no of patients	133	Abnormal urine	72	54
Average age (yr)	49	Abnormal electrocardiogram	99	74
Age range (yr)	26–72	Abnormal x ray*	80	60
Men	73	Previous infarctions (myocardial)	3	2
Women	60	Previous cerebrovascular accident	26	20
White	44	Funduscopic†		
Negro	89	Grade 1 and 2	76	57
Average systolic and diastolic blood pressure		Grade 3 and 4	52	39
Supine	217/132 mm Hg	Heart failure‡		
Upright	213/135 mm Hg	Class I	27	20
Average blood urea nitrogen (mg %)	27	Class II	27	20
(R * = 3–216)		Class III	18	14
Average glomerular filtration rate (cc /min) (R = 9–155)	80	Class IV	4	3
Average renal blood flow (cc /min) (R = 42–1706)	743			

* Refers to abnormalities of heart only
† Keith Wagener Barker classification
‡ Classification of American Heart Association
* Range of values

in the patients in this study The average renal clearance values of the entire group are considerably lower than the values in normal people

Fifty seven per cent of the patients had grade 1 and 2 funduscopic changes and 39 per cent had grade 3 and 4 changes Fifty seven per cent of the patients manifested signs and symptoms of heart failure varying from minimal to class IV The average supine and upright blood pressures for the group were 217/132 mm Hg and 213/135 mm Hg respectively In general there was a high incidence of vascular complications associated with hypertension indicative of rather severe disease

The results summarized in Table 2 show that in general the higher the diastolic blood pressure the greater the incidence of complications associated with hypertension This relationship is particularly noteworthy in the

TABLE 2 COMPLICATIONS OF HYPERTENSION DIVIDED ON BASIS OF DIASTOLIC BLOOD PRESSURE

	DIASTOLIC BLOOD PRESSURE							
	Subgroup A (100 to 120 mm Hg)		Subgroup B (121 to 140 mm Hg)		Subgroup C (above 140 mm Hg)		TOTAL	
DATA	No	%	No	%	No	%	No	%
Patients	34		55		44		133	
Abnormal urine	10	29	25	45	37	84	72	54
Abnormal electrocardiogram	26	76	34	62	39	89	99	74
Abnormal x ray	14	41	30	55	36	82	80	60
Previous infarction	1	3	0	0	2	5	3	2
Previous cerebrovascular accident	3	9	11	20	12	27	26	20
Funduscopic*								
Grade 1 and 2	26	76	36	65	14	32	76	57
Grade 3 and 4	5	15	17	31	30	68	52	39
Heart Failure†								
Class I	5	15	18	33	4	9	27	20
Class II	9	26	11	20	7	16	27	20
Class III	3	9	6	11	9	20	18	14
Class IV	1	3	2	4	1	2	4	3

* Keith Wagener Barker

† Classification of American Heart Association

roentgenographic evidence of cardiomegaly the incidence of cerebrovascular accidents the incidence of grade 3 and 4 eyeground changes and the incidence of abnormal findings in the urine The incidence of electrocardiographic changes and heart failure did not appear to be closely related to the degree of diastolic hypertension but rather appeared to be related in part to age

In Table 3 the patients are divided into subgroups on the basis of the

TABLE 3 COMPARISON OF COMPLICATIONS OF HYPERTENSION DIVIDED ON BASIS OF INITIAL GLOMERULAR FILTRATION RATE

	GLOMERULAR FILTRATION RATE cc /min									
	Subgroup I (above 100)		Subgroup II (80 to 99)		Subgroup III (40 to 79)		Subgroup IV (below 40)		TOTAL	
DATA	No	%	No	%	No	%	No	%	No	%
Patients	39		29		48		17		133	
Abnormal urine	14	36	16	55	29	60	13	76	72	54
Abnormal electrocardiogram	26	67	21	72	37	77	15	88	99	74
Abnormal x ray	19	49	19	66	29	60	13	76	80	60
Previous infarction	0	0	1	3	2	4	0	0	3	2
Previous cerebrovascular accident	6	15	5	17	11	23	4	24	26	20
Funduscopic										
Grade 1 and 2	24	62	21	72	24	50	7	41	76	57
Grade 3 and 4	12	31	8	28	22	46	10	59	52	39
Heart failure*										
Class I	11	28	9	31	6	13	1	6	27	20
Class II	8	21	5	17	8	17	6	35	27	20
Class III	3	8	6	21	7	15	2	12	18	14
Class IV	0	0	1	3	2	4	1	6	4	3

* Classification of American Heart Association

glomerular filtration rate at the time of study Subgroup I contains 39 patients (29 per cent of the total) with a glomerular filtration rate of 100 cc/minute or more which could be considered normal The average blood urea nitrogen (BUN) for this group was 15 mg per cent the average glomerular filtration rate was 118 cc/minute the average renal blood flow was 1111 cc/minute all of these values are normal The average upright blood pressure for this subgroup was 200/129 mm Hg with a mean blood pressure of 153 mm Hg In subgroup II (29 patients with a glomerular filtration rate of 80 to 99 cc/minute) the average values were 17 mg per cent for the BUN 89 cc/minute for the glomerular filtration rate and 809 cc/minute for the renal blood flow Thus the crude average blood pressure for this group with minimal depression of renal function was approximately the same as it was for the patients in subgroup I with entirely normal renal func

TABLE 4 COMPARISON OF RENAL STATUS IN HYPERTENSIVE PATIENTS OF VARIOUS AGE GROUPS

DATA	SUBGROUP I (to age 40)	SUBGROUP II (41 55)	SUBGROUP III (above age 55)	TOTAL
No of patients	28	67	38	133
Per cent of total patients	21	50	29	100
Average age (yr)	35	48	61	49
Men	14	36	23	73
Women	14	31	15	60
White	10	23	11	44
Negro	18	44	27	89
Blood pressure supine				
Average systolic	206	218	223	217
Average diastolic	136	132	129	132
Average mean	159	161	160	160
Blood pressure upright				
Average systolic	203	211	223	213
Average diastolic	139	135	132	135
Average mean	160	160	162	161
Average blood urea nitrogen (mg %)	25	27	28	27
Average glomerular filtration rate (cc/min)	85	78	80	80
Average renal blood flow (cc/min)	774	754	703	743

tion The corresponding values in subgroup III (glomerular filtration rate 40 to 79 cc/minute) were BUN 25 mg per cent glomerular filtration rate 62 cc/minute and renal blood flow 593 cc/minute indicating a more severe vascular deterioration as indicated by the depressed renal function In subgroup IV (glomerular filtration rate below 40 cc/minute) the average BUN was 72 mg per cent with a glomerular filtration rate of 27 cc/minute a renal blood flow of 212 cc/minute and a mean blood pressure of 169 mm Hg The degree of renal damage was not strictly related to the degree of blood pressure elevation but the duration of the hypertensive vascular disease was not taken into account in the analysis of these data

The duration of the blood pressure elevation is no doubt an important consideration in determining the degree of renal damage present at any specific time in the natural history of the disease Unfortunately it was impossible to determine the duration of disease with any accuracy in these

TABLF 5 COMPARISON OF RENAL STATUS IN HYPERTENSIVE PATIENTS BASED ON SEX AND RACE

S X	NO	%	A E (1)	BLOO REA NITROGEN (mg)	GLOMERLLAR FILT ATION R TE (c /m)	REN L BLOOD FLO V (c /m)	CONT OL BLOO PR URE SUPINE S	D	M	UPRIGHT S	D	M
I M												
A N g	41	56	52	31	7	715	212	130	157	210	132	158
B Wh t	32	44	48	32	3	662	27	145	172	218	146	1 0
T t l A + B a rag	73		50	31	5	691	218	136	163	13	138	163
W m n												
A N gro	48	80	48	19	88	813	210	1 6	154	209	130	156
B Wh t	12	20	51	28	6	52	35	136	169	223	14	171
T t l A + B r ge	60		49	21	85	801	215	1 8	157	213	13	159
T tal 1 + 2 ge	133		49	27	80	743	217	132	160	213	135	161
R												
N g	89	67	50	5	83	769	211	1 7	155	209	131	157
Whit	44		49	31	74	686	29	14	171	2 0	144	169

Not S = Sy tol blood p es e
D = D t lie bl d p n
M = Mean blood p es (d t l c + 1/3 p l p e)

patients A progressive rise in mean blood pressure can be correlated with a fall in the glomerular filtration rate (Figs 1 and 2) and renal blood flow and an elevation of the blood urea nitrogen The results given in Table 3 show that there is a greater incidence of complications of hypertension as the glomerular filtration rate and renal blood flow are reduced indicating increasing generalized vascular involvement It would appear that the glomerular filtration rate is a fair indication of the degree of vascular deterioration that has occurred throughout the body

In Table 4 the patients are subdivided on the basis of age Three age groups were chosen arbitrarily and consisted of 28 patients (21 per cent) age 40 years or less 67 patients (50 per cent) age 41 to 55 and 38 patients (29 per cent) above the age of 55 The data in Table 4 show that age did not influence the renal hemodynamics in the patients studied in this series The BUN glomerular filtration rate renal blood flow and mean blood pres

TABLE 6 VITAL STATISTICS RENAL HEMODYNAMICS AND COMPLICATIONS ON 32 PATIENTS WITH MALIGNANT HYPERTENSION

DATA	VALUES	COMPLICATIONS	NO OF PATIENTS	%
Total no of patients	32	Abnormal urine	26	81
Average age (yr)	44	Abnormal ECG	30	94
Age range (yr)	26–66	Abnormal x ray	26	81
Men	20	Previous infarction	2	6
Women	12	Previous cerebrovascular accident	5	16
White	20	Funduscopic		
Negro	12	Grade 1 and 2	0	0
Average systolic and diastolic blood pressure		Grade 3 and 4	32	100
		Heart failure		
Supine	239/150 mm Hg	Class I	2	6
Upright	233/151 mm Hg	Class II	7	22
Average blood urea nitrogen		Class III	3	9
mg % (R = 7–99)	34	Class IV	2	6
Average glomerular filtration rate cc /min (R = 18–146)	66			
Average renal blood flow cc /min (R = 118–1484)	572			

sure were almost identical in the different age groups These results differ somewhat from those generally found by other investigators who report more advanced renal involvement in the younger patient Apparently *the degree of renal damage resulting from blood pressure elevation overshadowed the effects due to age*

The data did show that there was a higher incidence of abnormal electrocardiographic (79 per cent as compared to 64 per cent) and x ray findings (68 per cent as compared to 50 per cent) in the older age group (subgroup III) as well as a slightly higher incidence of previous myocardial infarctions and cerebral vascular accidents (26 per cent as compared to 11 per cent) All of these findings can be explained on the basis of a higher incidence of associated arteriosclerosis occurring in the older age group which may not be closely related to the blood pressure elevation In contrast to these findings a higher incidence of grades 3 and 4 funduscopic changes occurred in the younger age group (50 per cent as compared to 26 per cent)

In Table 5 the observations are analyzed on the basis of race and sex of the patients There was no significant race or sex difference in the average renal function studies The average values for all groups were below the normal range The mean blood pressure was highest in the white men and white women as compared to the Negro patients Also there was a slightly higher incidence of complications of hypertension in the white male patients

Table 6 summarizes the vital statistics renal hemodynamics and complications of hypertension in thirty two patients with malignant hypertension The average age was 44 years with a range of 26 to 66 There were 20 men and 12 women Twelve were Negro and 20 were white The average BUN was 34 mg per cent the average glomerular filtration rate 66 cc /minute

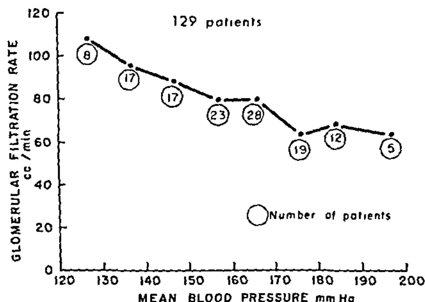


Fig 1 The average values for glomerular filtration rate compared to increasing severity of hypertension as estimated by mean blood pressure There is a greater reduction in glomerular filtration rate in those patients who show the greatest increase in blood pressure thus indicating a direct relationship between the severity of the blood pressure elevation and the renal vascular deterioration (From Moyer *et al* Am J Med *24* 177 1958)

and the average renal blood flow 572 cc /minute There was a high incidence of complications Eighty one per cent had abnormal urinary findings 94 per cent had abnormal electrocardiograms and 81 per cent had abnormal heart size by x ray examination of the chest Six per cent of the patients had had previous myocardial infarctions and 16 per cent had had previous cerebral vascular accidents All of the patients showed grade 4 funduscopic changes by the Keith Wagener Barker classification The average blood pressure for the group was 239/150 mm Hg and 233/151 mm Hg with the patients in the supine and upright positions respectively

DISCUSSION

The average glomerular filtration rate of 80 cc/minute and renal blood flow of 743 cc/minute for this group of patients with hypertension are below these same values of 131 cc/minute and 1209 cc/minute respectively for a group of normal individuals as reported by Smith and his associates[4,5] Although the absolute figures obtained in our series differ somewhat from those reported by others the results in general are in agreement[6-9] Not only does reduced renal function occur in patients with hypertension but

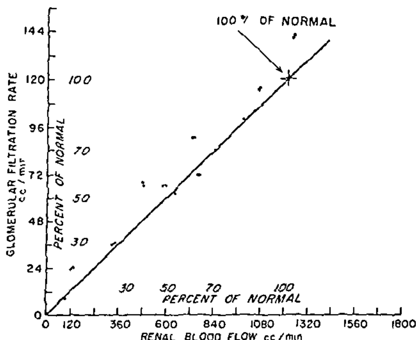


Fig 2 Glomerular filtration rate plotted against renal blood flow (PAH clearance) (expressed as per cent of normal) in patients with hypertension Renal blood flow as reflected in PAH clearance appears to be slightly more depressed than glomerular filtration rate as reflected in inulin clearance This may be due in part to decreased extraction of PAH The directional changes indicate a parallel reduction in glomerular filtration rate and renal blood flow with progressive renal damage (From Moyer *et al* Am J Med 24 177 1958)

there is also a rather definite correlation between the severity of the hypertension based upon diastolic blood pressure elevation and the glomerular filtration rate (Fig 1) and renal blood flow decrease (Fig 2) accompanied by a rising BUN (Fig 3) The average values for glomerular filtration rate and renal blood flow in those patients with mild elevation in blood pressure (diastolic less than 120 mm Hg) were normal and indeed early renal involvement would have escaped detection if special clearance tests had not been used. The lower incidence of complications of hypertension in this group is evidence for early though minimal generalized vascular involvement Evidence that the disease process is one of increasing generalized

vascular involvement is borne out by the patients in subgroups B and C (Table 2) who show an increased incidence of complications associated with a rise in blood pressure and a fall in renal function (Figs 1 and 2) This reduction in renal function is progressive especially in the patient with malignant hypertension (Fig 4)

The fact that hypertension is not always accompanied by renal involvement has been shown by other investigators and has been verified in this series There are instances in which hypertension is not accompanied by changes in the renal vasculature This probably depends on severity and

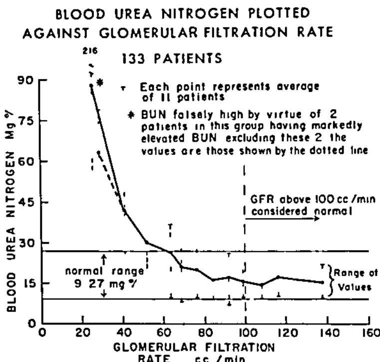


Fig 3 Glomerular filtration rate plotted against blood urea nitrogen Blood urea nitrogen is not elevated significantly until the glomerular filtration rate is reduced below approximately 70 cc per minute From this point on there is a progressive rise in blood urea nitrogen as the glomerular filtration is reduced (From Moyer *et al* Am J Med 24 177 1958)

duration of the blood pressure elevation Thirty nine patients (29 per cent) had glomerular filtration rates above 100 cc/minute which we consider to be within the normal range The average glomerular filtration rate for this group was 118 cc/minute with a renal blood flow of 1111 cc/minute both within the range of normal The average blood pressure for this group was 200/129 mm.Hg with the patient in the upright position

Seventy one per cent of the patients had definite evidence of progressive renal involvement associated with a rising blood pressure (Table 3) suggesting a disease process which if not altered has a grave prognosis Evidence in support of this statement is presented in Table 3 which shows that there is a definite increase in the complications of hypertension in patients

who have increased renal vascular involvement as reflected in the depression in the glomerular filtration rate

Applied clinically these results and those of others offer evidence that benign and malignant hypertension ultimately leads to a decrease in renal function the latter having an accelerated course (Fig 4) The rather clear evidence that there is a progressive decrease in function which can be correlated with an increase in blood pressure as well as an increase in complications of hypertension suggests to us that treatment of this condition may be of value The observations indicate that the age at which diastolic hypertension appears or the sex and race in which it occurs have little influence on the progression of the disease process

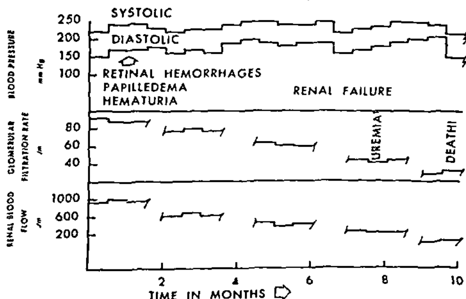


Fig 4 Untreated patient with malignant hypertension showing progressive deterioration in renal function as estimated by glomerular filtration rate and renal blood flow (From Moyer *et al* Am J Med 24 177 1958)

It is of interest to note that approximately one third of the functional reserve of the kidney as estimated by glomerular filtration rate was lost before a rise in BUN was noted When the glomerular filtration rate was above 70 cc /minute there appeared to be a random variation between 10 and 27 mg per cent in blood urea nitrogen (BUN) concentrations However when the glomerular filtration rate dropped below 70 cc /minute there was an increasing number of patients showing an elevated BUN (Fig 3) In fact when the BUN became elevated above 27 mg per cent only a small additional reduction in glomerular filtration rate appeared to result in severe renal decompensation

As the glomerular filtration rate was depressed a parallel reduction in renal blood flow was noted (Fig 2) the former being depressed somewhat

more than the latter This is consistent with many other observations on renal damage resulting from numerous causes

SUMMARY

The renal functional status of 133 patients with hypertension was determined by means of clearance tests An attempt was made to correlate the renal damage (and other complications of hypertension) with the blood pressure elevation

The results are in general agreement with those obtained by other investigators There is a definite decrease in glomerular filtration rate and renal blood flow for the group as a whole As the blood pressure increases there is a progressive decline in renal function and an increased incidence of complications in these patients Age sex and race did not appear to influence the severity of the disease process in this group of patients

Patients with malignant hypertension tended to have greater renal damage in association with more severe generalized vascular disease than did patients who did not have papilledema

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Discussion

FRANCIS WOOD *Moderator*

QUENTIN DEMING
WILLIAM DOCK
EDWARD FREIS
WILLIAM LIKOFF
MARVIN MOSER
JOHN H MOYER
PAUL NOVACK
H MITCHELL PERRY JR
PAUL RHOADS
HENRY SCHROEDER
SHELDON SOMMERS

DR WOOD Dr Moyer if your explanation for relief of headache with aminophylline in hypertensives is correct you should be able to get equivalent results with ergotamine tartrate Can you?

DR MOYER Not very effectively Even if ergotamine were effective the explanation for the response would not be apparent since the mechanism of action of the drug is not well understood

DR NOVACK We did some studies on ergotamine with Dr Shenkin which we never published We could not demonstrate that the drug had any effect on the cerebral circulation

DR MOYER Dr Wood referred to the effect of aminophylline Table 1 is a summary of some observations that we made in a group of patients with severe hypertensive headaches who were given 0 5 gm of aminophylline intravenously The headache was relieved in all but one of these patients within seconds after the drug was given Since the cerebral blood flow and cerebral spinal fluid pressure decreased so dramatically we could only conclude that the relief of symptoms was probably due to altered cerebral hemodynamics Cerebrovascular resistance increased uniformly and cere

TABLE 1 THE EFFECT OF AMINOPHYLLINE ON CEREBRAL HEMODYNAMICS IN PATIENTS WITH HYPERTENSIVE HEADACHES

	NORMAL	CONTROL OBSERVATION (Hyper tension)	AFTER AMINO PHYLLINE	PER CENT OF CONTROL	P VALUE LESS THAN
Mean blood pressure	85	151	141	93	NS
Cerebral blood flow (cc /100 gm brain/min)	54	53	36	68	01
Cerebrovascular resistance	1 6	3 0	4 3	143	03
Cerebral oxygen uptake 100 gm brain/min	3 3	3 6	3 3	92	NS
Cerebral A VO		7 0	9 2	131	
Cerebrospinal fluid pres ure (mm H O)		210	132	63	08

NS = not stati tically significant

bral oxygen uptake was not altered Cerebral arteriolar constriction would result in a decrease in vascular volume in the brain and consequently a reduction in pressure within the bony framework of the head (Table 1) It is of interest that aminophylline reduces cerebral blood flow rather than increases it

I should like to ask Dr Freis if his patients specifically respond to having their blood pressure taken with an elevation in blood pressure or do they respond to any annoying distressful situation in a similar way? I am reopening the problem as to whether we should treat patients whose blood pressure is normal at home but elevated in the doctor s office

Dr Wood May I get into this argument before Dr Freis does? The problem of whether a patient has an elevated blood pressure is more difficult than you may think I never do anything with patients at the time of their first visit because by the third time I see them their actual blood pressure is 15 to 20 mm Hg lower and they may not be hypertensive at all I am interested in whether these are the patients who do not get cardiac enlargement who do not develop difficulties because they have normal blood pressures when they are in more normal surroundings Dr Freis why doesn t the heart enlarge in all patients with hypertension? Some of the evidence that you presented suggested that this should occur regularly

Dr Freis I think that the heart probably does enlarge in most patients with elevated basal arterial pressure When cardiac enlargement does not occur it is probably in those patients who have blood pressure elevation only at certain times as for example when coming into the doctor s office This is why I think that home blood pressures are so important

Dr Dock In severe hypertension the heart shadow by x ray frequently does not enlarge at all The weight of the left ventricle increases but the capacity of the left ventricle decreases It is only when the heart fails that the heart shadow increases

Dr Moyer I would like to get back to Dr Freis again and ask him if his patients specifically get a blood pressure elevation just when they have their blood pressure taken or whether this is a reaction to all stressful situations

Dr Freis I do not think that they get the same reaction to all stressful situations At home some of them have taken their pressures when they were angry that is irritated without being fearful This did not seem to raise their blood pressure very much But when there was an element of fear involved pressures were raised

Dr Moyer Isn t most anxiety a fear reaction? I can t accept the fact that the reaction to the blood pressure cuff is specific and that these patients wouldn t get an increase in blood pressure to a situation producing a similar psychological response under any circumstances I d like to stress this from a different viewpoint Some patients actually have their highest blood pressures in the hospital It is not at all uncommon to have such a patient regulated on drugs and then have hypotensive symptoms at home because he is more relaxed.

DR PERRY This also may happen on vacations Dr Wood do you take blood pressures on your patients? I m only saying that because I seldom take a blood pressure any more

DR WOOD Yes I take them all the time Why—are you trying to put me into a bad spot?

DR PERRY I m trying to relieve you of the labor of taking blood pressures and have you turn them over to a technician or nurse I feel very strongly that my own blood pressures mean very little except that they are up or down

DR WOOD Well I d say that I have a very soothing effect on my patients

DR DEMING I would like to ask Dr Schroeder about the incidence of atherosclerosis in Asiatics who are hypertensive

DR SCHROEDER I think the incidence of coronary atherosclerosis in the Japanese over the age of 50 in Tokyo and Nagasaki is roughly the same as in Boston and Minneapolis The incidence is less in people under 50 a coronary in the young is quite uncommon Coronary disease coronary occlusion or myocardial infarction is the first cause of death in medical examiners cases at all ages in patients with hypertension As a matter of fact a rupture of the myocardium is several times more common in Japan than it is here There are areas where autopsy evidence of atherosclerosis is uncommon In Thailand for example there seems to be a large percentage of people showing no atherosclerosis in the aorta not even fatty streaks

DR. MOYER I would like to ask Dr Likoff and Dr Dock a question How do you go about differentiating the electrocardiographic changes due to hypertension and those due to arteriosclerosis?

DR DOCK Well I m not an electrocardiographer but I think the only change you would expect from hypertension would be deviations in the voltage in the precordial leads which presumably show that one is dealing with larger, thicker muscle fibers This would produce big R waves in V 3 V 4 V 5 or even V 6 You would get this in aortic stenosis with normal pressure or in hypertension uncomplicated by any coronary disease This is the only thing I think you would expect in hypertension and aortic stenosis and all the other changes that may be seen should be attributed to damage done to the coronary system

DR LIKOFF The changes that are noticed in the electrocardiogram both in coronary atherosclerosis without infarction and in hypertension involve repolarization Regardless of the etiology of these changes they basically represent an alteration in metabolism precipitated by thickened muscle cells which have outgrown their blood supply or by arterial disease which has decreased blood supply independently It would appear therefore that one cannot empirically decide which of these repolarization changes are the result of one process or the other

DR DOCK Do you think that in chronic hypertension and coronary atherosclerosis you get exactly the same changes over the left ventricle?

DR LIKOFF The S T segment changes and the T wave inversions—for example of subendocardial ischemia—are quite identical to those seen in chronic hypertension

DR WOOD I would like to answer the question in a more simple fashion On one hand one may see the electrocardiogram of left ventricular hyper trophy on the other the tracing of myocardial infarction In the majority of instances however the electrocardiograms in hypertension are not clear cut patterns of either situation Thus classifying hypertensive patients on the basis of the tracing is not very satisfactory

DR MOYER I would suspect that about 70 per cent of the ECG changes come into that gray zone you described

DR MOSER Do we agree that the S T segment changes we see in leads V 3 4 5 and 6 and in lead 1 in young hypertensives are a part of the hyper tensive picture?

DR WOOD I think this is one of the ECG abnormalities related only to hypertension if the patient has not had digitalis There are other changes which are less definitive Are there any questions that anybody in the audi ence would like to ask?

AUDIENCE MEMBER Is the increase in QRS duration seen in hypertension due to coronary artery disease?

DR LIKOFF In view of the preceding and present questions I should restate my position I agree that certain changes in the ECG may be caused by hypertension without involving coronary artery disease However this cannot always be determined categorically Certainly the early prolongation of the QRS complex may be the result of an increase in muscle mass alone without coronary artery disease

DR WOOD Dr Schroeder why do you treat blood pressure elevation?

DR SCHROEDER Hypertension is characterized by a generalized vaso spasm Yet we attempt to classify it by measurements of the height of the blood pressure or by measurements of the severity of the accompanying atherosclerosis We should try to think of the disease in terms of the patient What are we going to treat? We cannot treat atherosclerosis We *can* lower blood pressure Therefore you must determine whether high blood pressure is harming a specific patient and whether after you have started treating him he feels better If he doesn t feel better you must be sure that he is going to live longer or you haven t any right to treat him You really make these people feel worse many times when you first begin treatment If you stop treatment later in the program you can also cause a great deal of trouble In short the need for therapy must justify the difficulties that may ensue with its institution

DR. WOOD Some patients begin to feel ever so much better under therapy whereas others frequently feel very bad I believe the point has been well taken by Dr Schroeder

DR MOYER Side effects associated with blood pressure reduction are very variable Generally however the patient who has the most severe symptoms resulting from hypertension tends to have very few complaints relative to undesirable effects when his blood is lowered These patients are very grateful for the relief of their headaches improvement in heart failure symptoms and so forth It is the patient who is asymptomatic prior to treatment who complains most bitterly of side effects associated with drug administration

DR FREIS I think the question posed is concerned with the fact that we should improve our methods of lowering blood pressure With the use of chlorothiazide Rauwolfia and hydralazine one can achieve reduction of blood pressure in a large number of patients without producing the lethargy and fatigue observed with the ganglionic blocking agents The idea of lowering blood pressure is a good one and it is just a matter of finding better ways of accomplishing this without making the patient feel so uncomfortable

DR DEMING The speed with which blood pressure is reduced has a bearing on how a patient feels under treatment In patients with malignant hypertension most of us feel impelled to move fast But these are the small minority of the patients seen by physicians If you make those who do not have malignant hypertension feel worse you have gone too fast That does not imply it was wrong to treat the patient The therapist should take months rather than days to build the therapeutic program in the mild hypertensive

DR MOYER This is the reason I prefer to initiate therapy in these patients

DR MOSER I think it all boils down to a decision as to what we are justified in doing based on what we know about prognosis With the data presently available I think we are all able to judge in broad terms at least just how much risk we are justified in taking with the patient before we lower his pressure The main trouble with medical therapy is that if the patient complains and if we do not have a steady hand we might forget that we were justified in the treatment and stop it I think that if we accept the idea of being justified in view of the poor prognosis and stick to a steady kind of treatment we will accomplish the purpose

DR WOOD It is fairly easy to justify potent drug therapy in malignant hypertension There is no alternative It is a different matter with patients who do not appear to be ill aside from an elevation in their blood pressure

DR. SCHROEDER I don t believe in treating numbers However if we revert numbers to normal without making the patient uncomfortable or harming him he should be better off over the next twenty years

DR FREIS Although mortality statistics in long term treated patients with mild hypertension are not available other well documented data are available For example with the evidence that hypertension accelerates atherosclerosis and the evidence that high pressure in the arterial tree produces arteriosclerosis and hypertrophy of the heart then isn t it logical to con

clude that lowering of the blood pressure which produces these alterations is indicated irrespective of severity?

DR MOYER Carrying this a step farther our observations on kidney function indicate that the degree of renal damage is directly proportional to the elevation in mean arterial blood pressure This then indicates that using the degree of blood pressure elevation as an index of severity is also an indication of the severity of clinical hypertensive vascular disease I would like to ask Dr Rhoads whether he thinks antihypertensive therapy is of any value in patients with hypertension due to pyelonephritis over and above specific therapy for the infection

DR RHOADS I think such patients need to have their hypertension treated as well as their urinary tract infection I do not know whether reducing the high blood pressure reduces the tendency to pyelonephritis

DR MOYER Suppose you had a patient with glomerulonephritis who did not have a very high BUN but who had a marked hypertension Would you treat that patient?

DR RHOADS Yes

DR WOOD Is there any evidence that various pain syndromes in different areas in the body in hypertensives are due to muscle ischemia as a result of small artery damage?

DR MOYER I believe that Dr Sommers has described doing muscle biopsies in which he found a decreasing number of arterioles depending on the severity of the hypertension

DR SOMMERS Yes this is so The fact is that the damage produced by hypertension is thought to be due to ischemia rather than infarction This is true in the brain the heart the kidneys and other areas of the body

DR WOOD Perhaps this explains the precordial pain which is so common in hypertensives Dr Moyer does the renal vasculature in the patient with renal damage due to hypertension respond to stress in the same way that the renal vessels do in a normal individual?

DR MOYER I cannot answer this in a definitive manner but I would say that it does For example we have studied the effect of passive head up and ambulation on renal hemodynamics and water and electrolyte excretion When the patient stands or walks there is sometimes some reduction in blood pressure but the renal vessels contract quite markedly in an attempt to maintain an adequate circulation in the brain and thorax This results in reduction in renal blood flow and glomerular filtration rate An acute decrease in water and sodium excretion follows The response is qualitatively the same for all patients irrespective of the severity of the renal vascular damage The responses are summarized in Figures 1 to 5 and Table 2

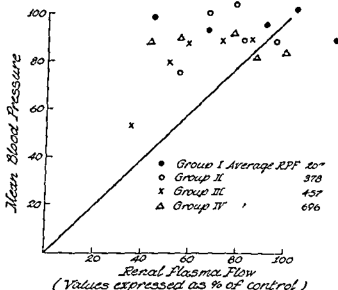


Fig 1 Effect of head up tilting in untreated patients with hypertension Mean blood pressure for each patient is plotted against renal plasma flow and the values after tilting are expressed in per cent of the control observations There is a tendency toward blood pressure reduction but renal plasma flow is reduced out of proportion indicating an increase in renal vascular resistance Patients with severe renal vascular damage (Group 1) respond essentially the same way as patients with less severe disease (From J Lab & Clin Med 45 179 1955)

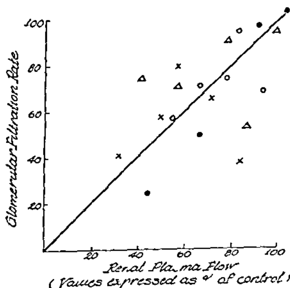


Fig 2 The effect of head up tilt on glomerular filtration rate as compared to renal plasma flow in untreated patients with hypertension The values after tilt are expressed in per cent of the control observations There is approximately an equivalent reduction in glomerular filtration rate and renal plasma flow Symbols ●—patients in Group I O—patients in Group 2 x—patients in Group 3 Δ—patients in Group 4 (From J Lab & Clin Med 45 179 1955)

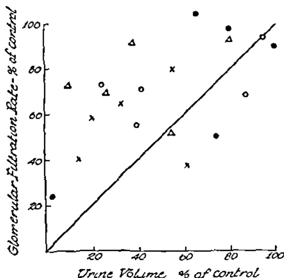


Fig 3 Effect of tilting on urine volume as compared to glomerular filtration rate in untreated patients with hypertension Values are expressed in per cent of control observations There was a reduction in urine volume out of proportion to the depression in glomerular filtration rate Symbols ●—patients in Group 1 O—patients in Group 2 x—patients in Group 3 Δ—patients in Group 4 (From J Lab & Clin Med 45 179 1955)

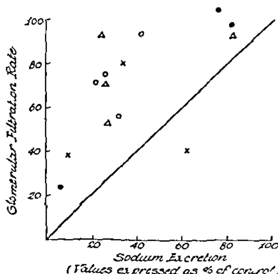


Fig 4 Effect of tilting on sodium excretion as compared to glomerular filtration rate in untreated patients with hypertension Values after tilt are expressed as per cent of control observations Sodium excretion is depressed out of proportion to the reduction in glomerular filtration rate Symbols ●—patients in Group 1 O—patients in Group 2 x—patients in Group 3 Δ—patients in Group 4 (From J Lab & Clin Med 45 179 1955)

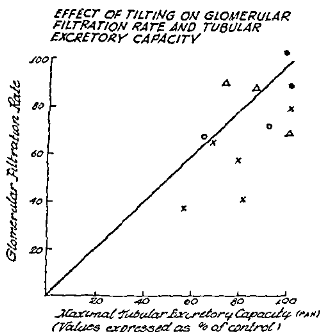


Fig 5 Effect of tilting on glomerular filtration rate as compared to maximal tubular function (Tm PAH) in untreated patients with hypertension Values after tilt are expressed in per cent of control observations Generally glomerular filtration rate is reduced out of proportion to Tm PAH Symbols ●—patients in Group 1 O—patients in Group 2 x—patients in Group 3 Δ—patients in Group 4 (From J Lab & Clin Med *45* 179 1955)

TABLE 2 SUMMARY OF RENAL RESPONSE TO AMBULATION AS COMPARED TO 60 DEGREE HEAD UP PASSIVE TILT EXPRESSED AS MEAN VALUES

	RESPONSE TO AMBULATION			RESPONSE TO TILT		
FUNCTION STUDIED	R	A	A/R × 100	R	T	T/R × 100
Mean blood pressure (mm Hg)	159	161	101	141	126	89
Glomerular filtration rate (ml /min)	73	65	89	75	51	68
Renal plasma flow (ml /min)	449	380	85	427	292	68
Tubular excretory capacity (mg /min)	63	57	90	59	47	80
Hematocrit	44	45	102	41	43	105
Renal blood flow (ml /min)	801	695	87	748	528	71
Renal vascular resistance	0 247	0 302	122	0 286	0.357	125
Urine volume (ml /min)	13 3	9 6	72	7 7	4 1	53
Sodium excretion (μEq /min)	506	369	73	421	164	39
Potassium excretion (μEq /min)	176	182	103	78	47	60

R = Recumbent—Control A = Ambulatory T = Head up tilt
(From J Lab & Clin Med *45* 179 1955)

Part II

BASIC CONCEPTS OF THE ETIOLOGY OF HYPERTENSION

Laboratory and Clinical Observations on the Renal Origin of Hypertension

ARTHUR GROLLMAN

University of Texas Southwestern Medical School

The concept that hypertension may be of renal origin is now generally accepted. The points of controversy are the frequency with which hypertension is of renal origin and whether or not hypertension may also be extrarenal in origin. When hypertension is induced by the application of a clamp to one renal artery and removal of the contralateral kidney, by the application of a membrane or figure of eight ligature to one kidney and the removal of the contralateral organ, or by some other direct manipulation of the kidney, few deny that it is experimental hypertension of renal origin. Likewise spontaneously occurring hypertension in the human accompanied by evident morphologic damage of the kidney, as in the nephritides, and a plaque on the renal artery or an infarct of the kidney associated with hypertension are generally accepted as instances of hypertension of renal origin. However, in the majority of instances of hypertension observed clinically, e.g., in essential hypertension where no such morphologic evidence of damage is evident, most observers question the renal origin of the disease. Many instances of experimental hypertension, e.g., that induced by nephrectomy or by the chronic administration of corticosteroids are also considered by many to be of extrarenal origin.

Conclusions regarding the pathogenesis of hypertension in the human are dependent upon experimental observations in laboratory animals. However, many still deny the existence of a close relationship between human and laboratory induced hypertension. This refusal to concede the similarity between the two, however, is unjustified since the disease in man as well as in the animal has the same clinical, hemodynamic and pathologic features. In fact, few disorders in the human which are recognized as having a counterpart in the experimental animal approach so closely in their identity hypertension as it affects different species.[1]

The view has been expressed that hypertensive disease as it affects the human spontaneously and as it is produced in the experimental animal is always of renal origin. The acceptance of this view, however, presupposes an exact definition of what is meant by hypertensive disease. One cannot consider any elevation in blood pressure as representative of hypertensive disease but must recognize the lability of the blood pressure as a variable hemodynamic function subject to change as a result of many causes.[3] Such temporary elevations in blood pressure as are induced by corticosteroid administration in animals, overloading with saline following removal of the kidneys and similar experimental procedures inducing an elevation in blood pressure would not be considered true hypertensive disease but merely

elevations in blood pressure reflecting a hemodynamic disturbance Clinically likewise the acute and temporary elevation in blood pressure induced by nervous disturbance the systolic hypertension reflecting the inelasticity of the arterial system in atherosclerosis the increased pressure of the hyperthyroid individual which reflects the increase in metabolism and similar instances of an elevation in blood pressure would also be excluded

With the limitations described above hypertensive cardiovascular disease may be considered a disease entity defined hemodynamically by a chronic elevation in blood pressure secondary to a generalized increase in peripheral resistance accompanied by a normal cardiac output and pathologically by cardiac hypertrophy and arteriolar thickening Accepting these criteria one can support the hypothesis that all hypertension experimental as well as clinical is renal in origin

If the renal origin of hypertension is accepted it is clear from experimental as well as clinical observations that two types of this disorder exist The form most commonly stressed but which from the available evidence would seem to occur only rarely in man is due to the liberation of a pressor agent In such instances removal of the source of this pressor agent would result in cure of the disease On the other hand in the majority of cases particularly in so called essential hypertension no such simple explanation accounts for the observed facts a more tenable theory in line with the known facts is that this disease is due to the deficiency of an essential agent necessary for the maintenance of the normotensive state This agent like the pressor agent is humoral in action

Braun Menendez[4] has postulated the existence of a renotropic agent extrarenal in origin to account for those instances of hypertension not induced by angiotensin the pressor agent derived from the kidney Others[5] assume that the kidney produces a humoral agent a deficiency of which results in hypertension

Obviously much more work is necessary to establish the extent of the role of the kidney in the pathogenesis of hypertension The available data suffice however to render plausible the hypothesis that the kidney is the organ responsible for the specific disorder designated as hypertensive cardiovascular disease Many instances of hypertension not obviously of renal origin may be postulated to occur as a result of a renal defect the exact nature of which has not been established

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Sympathetic and Adrenal Medullary Factors in Hypertension

J RICHARD CROUT

Section of Experimental Therapeutics National Heart Institute

The role of the sympathetic nervous system in normal cardiovascular physiology is well established Pressoreceptors in the carotid sinus and aortic arch closely monitoring central arterial pressure send afferent impulses to the vasomotor center of the brain stem which in turn regulates arteriolar tone and cardiac function through the autonomic nervous system Both vaso constrictor and vasodilator fibers are present in the sympathetic system but normal arteriolar tone is believed to be regulated by the adrenergic vaso constrictor fibers only Although both sympathetic cholinergic fibers and adrenal epinephrine may stimulate active vasodilatation in skeletal muscle beds during the generalized sympatho adrenal discharge in severe stress neither of these factors is thought to influence vascular tone significantly under normal circumstances [4]

The neurohumoral transmitter of the adrenergic system peripherally is considered to be norepinephrine [4] Although epinephrine was once thought to be the transmitter its presence in sympathetic nerves is probably in relationship to scattered chromaffin cells which do not participate in neurohumoral function [17] A considerable amount of 3 4 dihydroxyphenyl ethylamine (dopamine) also occurs in sympathetic nerves This compound is not known to participate in neurohumoral transmission however and is thought to serve only as the biologic precursor for norepinephrine [4] Nor epinephrine is synthesized within sympathetic tissue stored in granules located in the axon and released from these granules by the nerve impulse [4] Although the mechanism of storage and release is poorly understood re cent work suggests that norepinephrine is bound in the granule as a cat echolamine ATP protein complex which breaks down during release of the hormone [9] No quantitative data are available on norepinephrine turnover rates at nerve endings but the fact that the release of norepinephrine pro ceeds unimpaired during many hours of continuous nerve stimulation sug gests a rapid rate of synthesis [4]

If the sympathetic nerve to any given vascular bed is stimulated at a physiologic rate i e less than ten impulses per second [4] little norepi nephrine can be demonstrated in the venous return from that bed [1] Only at higher nonphysiologic impulse frequencies can considerable amounts of the transmitter be detected in the venous drainage It is thus unlikely that dis tant organs are significantly influenced by norepinephrine "overflow" into the blood stream under normal conditions That some norepinephrine does enter the circulation however is indicated by its presence in blood and urine The urinary excretion of norepinephrine is unchanged by adrenal ectomy suggesting that it is largely derived from sympathetic nerves

TRUE NEUROGENIC HYPERTENSION

An elevation of the blood pressure normally occurs during increased activity of the sympathetic nervous system If such sympathetic hyperfunction becomes sustained chronic neurogenic hypertension will result In man this rare abnormality may occur either through release of the vasomotor center from sinoaortic inhibition (as in bilateral glossopharyngeal nerve section) or through central stimulation of the vasomotor mechanism (as in certain intracranial tumors tabes dorsalis and the diencephalic hypertension syndrome)[19] The experimental counterpart of this neurogenic hypertension may be produced in animals by severing the moderator nerves injuring the hypothalamus or injecting kaolin into the cisterna magna[18 19]

This form of hypertension is characterized in general by great lability of the blood pressure increased cardiac output and little tendency toward the development of arteriolar lesions or marked cardiac hypertrophy[19] Furthermore the blood pressure falls to normal with correction of the basic neurologic lesion or with inhibition of sympathetic activity by ganglionic blockade or sympathectomy [19] Thus true neurogenic hypertension bears little resemblance to the primary human disease and is properly classified as a type of secondary hypertension

It is of interest that hypertension has been produced by buffer nerve section in dogs previously subjected to complete sympathectomy except for the renal and adrenal innervation and that the blood pressure of these animals returns to normal after renal nerve section[7] This suggests that increased sympathetic outflow may elevate the blood pressure through a renal mechanism as well as through a direct action on the heart and peripheral vessels The recently described production of hypertension by bilateral constriction of the carotid sinus areas in dogs may also be mediated by a neural mechanism[8] This experimental hypertension appears to resemble the primary human disease more closely than do other types of neurogenic hypertension If humoral factors can be excluded this may be the first demonstration of a neural mechanism producing a hemodynamic abnormality similar to that of human primary hypertension

PRIMARY HYPERTENSION

It is frequently postulated that sympathetic overactivity accompanies not only true neurogenic hypertension but also the primary hypertension of man at least in certain stages of the disease Evidence cited in favor of this concept includes the known adverse effect of psychic stress on the blood pressure and the known therapeutic benefit of measures which inhibit sympathetic function Experimental evidence from several sources however would suggest that over all sympathetic function may be normal in primary hypertension This evidence has been obtained from three general types of investigation studies of catecholamine excretion studies of arteriolar tone and studies of the cardiovascular reflexes in hypertension

The urinary excretion of norepinephrine has been shown to vary quite sensitively with changes in sympathetic function Thus the excretion is increased by physical exertion surgical trauma psychic stress and even by standing upright as compared to lying down Similarly it is decreased by bed rest by ganglionic blockade and in idiopathic orthostatic hypotension[2]

In the vast majority of cases of established primary hypertension however the catecholamine excretion has been found to be within normal limits The relatively high excretion shown by a few hypertensives suggests that sympathetic hyperfunction may occur in certain patients but is the exception rather than the rule One might speculate that the percentage of hypertensives with a high norepinephrine excretion (16 4 per cent) bears some relation to the percentage of patients showing an excellent response (return to normal blood pressure) to splanchnicectomy (22 8 per cent) or to total sympathectomy (27 4 per cent)[8, 1] However no correlated study is available to indicate whether the same type of patient would fall into both groups No careful evaluation has been reported of the norepinephrine excretion by labile hypertensives during periods of elevated pressure as compared to their more normal phases Available data on urinary catecholamines thus leave open the question of sympathetic hyperfunction in the early labile phase but weigh against a significant participation of this mechanism in the majority of patients with established hypertension

Considerable information on over all vasoconstrictor activity in hypertension has also been obtained from studies of arteriolar tone Most investigators in this area have found the peripheral vascular resistance across innervated limbs to be greater in established hypertensives than in normals[10, 16] A decrease in the vascular resistance can generally be achieved however by inhibiting the sympathetic discharge with ganglionic blockade or by stimulating vasodilatation with body heating This would indicate that at least part of the increased vascular resistance in hypertension is neurogenic in origin and acutely reversible Even after these vasodilating maneuvers however the peripheral vascular resistance of hypertensives may remain higher than that of normals subjected to the same stimuli[10, 16] suggesting that the remaining increment of abnormal resistance in hypertension is neither neurogenic in origin nor acutely reversible The magnitude of the neurogenic fraction of this increased vascular resistance has been difficult to assess and most experiments would suggest that it is quite variable from patient to patient

A third informative area of study relating to over all sympathetic function is that dealing with the cardiovascular reflexes in hypertension Detailed investigation of the sinoaortic buffer nerve mechanism has shown that this reflex mechanism functions in the renal hypertensive dog exactly as it does in normals i e it tends to resist acute changes of the blood pressure in either direction[13] The pressure it tends to maintain however is the elevated level established by the renal hypertensive mechanism The human hypertensive also maintains normal carotid sinus function[19] suggesting that a similar resetting" of the baroceptor occurs in man This tendency of the baroceptor mechanism to adapt to rather than to resist *chronic* changes in the blood pressure thus may favor the maintenance of hypertension once it has been established Reversibility of this neural adaptation is implied however by the fact that a renal hypertensive animal or patient can return to normal after removal of the offending kidney[13] Similarly a downward "resetting of the barostat" with effective antihypertensive treatment may account in part for the common observation that the hypertensive patient maintains his lowered pressure with less drug therapy than was required initially It should be emphasized that this sinoaortic adaptation implies *normal* over all sympathetic function in the presence of chronic hyperten

sion Hyper or hypoactivity of the sympathetics due to this reflex seems limited to periods of *acute* changes in the blood pressure

In summary these varied observations on catecholamine excretion arteriolar tone and the moderator reflexes would all seem to indicate essentially normal sympathetic function in most cases of established primary hypertension This generalization does not rule out the possibility that chronic sympathetic hyperfunction may be prominent in some cases nor does it imply that the usual hypertensive (or normotensive) patient is free of transient periods of excessive sympathetic activity Also this general conclusion need not conflict with evidence showing a profound influence of life stress upon the blood pressure but it should perhaps raise the question as to whether this influence of stress is mediated directly via the sympathetic nervous system

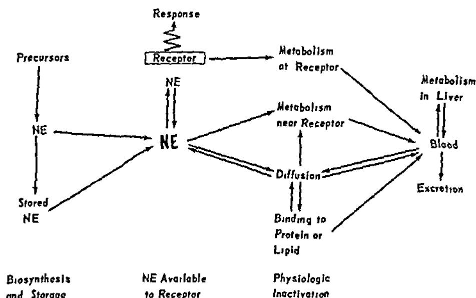


Fig 1

HYPER RESPONSIVENESS TO NOREPINEPHRINE

The inability to demonstrate sympathetic hyperfunction clearly and consistently in primary hypertension in no way excludes this system from participation in the pathogenesis of this disease The adrenergic vascular response is a function of the concentration of norepinephrine at the receptor site and thus it is subject to a number of influences besides norepinephrine production at the nerve ending A schematic representation of several influences on norepinephrine concentration near the receptor is shown in Figure 1 It is clear that even normal production of the transmitter by nerve endings may produce an exaggerated vasoconstrictor response if the vascular tree is supersensitive to adrenergic agents or if the physiologic inactivation of norepinephrine is impaired There is considerable current interest in the role of the e possible mechanisms in primary hypertension Studies relating to vascular reactivity will be considered first

The response of vascular smooth muscle to both constricting and dilating

humoral agents is profoundly modified by the sympathetic innervation As a general rule vascular responsiveness to humoral agents decreases as nervous control increases Thus as sympathetic influence over small vessels declines in passing from arterioles to precapillaries an increasing gradient of reactivity to humoral and metabolic stimuli appears [6] Normally the arterioles are largely under neural control while precapillaries function nearly autonomously in response to local changes in tissue metabolism In the intermediate segment the terminal arteriole considerable overlap of neural and humoral influence apparently occurs The concentration of a direct humoral vasoconstrictor necessary to produce hypertension through arteriolar constriction would be expected therefore to exert a prominent constrictor influence on the even more responsive precapillary Hypertension produced by such an agent should thus be characterized by constriction of all the muscular vessels of the arterial microcirculation including the precapillaries of the nailfold and bulbar conjunctiva Direct observation of these vessels has revealed that capillary ischemia does occur during a norepinephrine infusion or a paroxysmal hypertensive attack in pheochromocytoma but is not a feature of primary hypertension [6, 1] The selective narrowing of arterioles in human hypertension would thus suggest that the blood pressure is not elevated by so simple a mechanism as a circulating direct vasoconstrictor *provided* hypertensives maintain the normal gradient of small vessel reactivity to humoral stimuli

That normal vascular reactivity may not be so maintained in the hypertensive state however is suggested by the frequently observed supernormal blood pressure response of hypertensives to injected vasoactive substances [1] Vasoconstrictor agents such as norepinephrine as well as vasodilators like acetylcholine and nitroglycerine have been shown to produce greater than normal blood pressure changes in human and experimental hypertension In some animal studies this phenomenon has been noted to precede the appearance of high blood pressure while in others it has appeared only after full establishment of the hypertension Though repeatedly demonstrated by many investigators this augmented blood pressure response is not universally interpreted as showing increased vascular reactivity Folkow[9] and others point out from a consideration of Poiseuille's law that any given degree of muscular contraction might be expected to produce a greater vascular resistance in the presence of slightly thickened arterioles than would occur in normal vessels This explanation thus relates the altered blood pressure response to a structural mechanical abnormality of the vascular tree Mendlowitz however has noted the early appearance of an increased response to norepinephrine in normotensives treated with ACTH and adrenal steroids though hypertension was not present at the time [11] This suggests that a structural alteration of the vessel is not necessary to produce the phenomenon Also the mechanical explanation does not seem to account for the finding that the threshold dose of norepinephrine required to produce contraction in conjunctival and nailfold vessels is considerably less in hypertensives than in normals [6] The threshold infusion rate of epinephrine required to give just a response of the nailfold vascular bed in hypertensives[6] is in the reported range which may be achieved by the adrenal secretion after certain physiologic stimuli Thus in the presence of a sensitized vascular tree adrenal epinephrine might contribute to vasomotor activity at a secretion rate which would have little effect normally [4]

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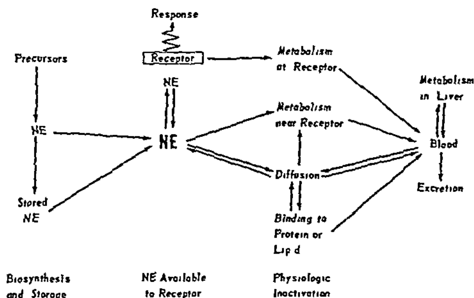


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The response of vascular smooth muscle to both constricting and dilating

enzymes simultaneously however might profoundly limit over all metabolism and increase the excretion of free and conjugated norepinephrine Inhibition of either enzyme should also be accompanied by a disturbance in the metabolism of other compounds which are substrates for one or both of these enzymes (e g serotonin tryptamine and dopamine) Although no comprehensive study has appeared comparing the metabolism of these compounds in hypertensives and normals preliminary unpublished studies in our laboratory have shown that oral serotonin is metabolized normally by patients with hypertension and that the excretion of free tryptamine is not increased over normal in hypertension Since these substrates are metabolized largely by monoamine oxidase these observations indicate no deficiency of this enzyme in hypertensives Furthermore monoamine oxidase inhibition in hypertensive patients produces no striking increase in the excretion of free norepinephrine or dopamine suggesting that the alternate pathway through catechol O methyl transferase is available for metabolism of these amines and, therefore is intact in hypertensives These preliminary data thus strongly suggest that no over all deficiency of either major enzyme involved in norepinephrine metabolism exists in hypertension It must be considered however that an enzymatic defect limited to the receptor site might impair local degradation of the transmitter without producing a change in the over all metabolism of the compound

This latter field of investigation though of current speculative interest remains largely unexplored in the human The recent paradoxical finding that inhibition of monoamine oxidase in man may be associated with orthostatic hypotension rather than hypertension [9] also indicates that the role of "amine inactivating" enzymes in neurovascular function may be considerably more complex than is appreciated at present

CONCLUSIONS

Although the clinical course of some hypertensive patients suggests a prominent neurogenic component there is little experimental evidence to support the view that sympathetic overactivity plays a major role in the pathogenesis of primary hypertension in most cases of the disease Over all sympathetic function though highly variable between patients appears on the average to be essentially normal This maintenance of normal sympathetic function in the presence of an elevated blood pressure is facilitated by an adaptation of the sinoaortic pressoreceptors to the higher levels of pressure in the hypertensive patient This adaptation may be considered a major abnormality of sympathetic function in a sense for it converts a reflex which normally resists hypertension into a mechanism tending to maintain the existing elevated level of pressure

Sympathetic hyperactivity need not be invoked however to implicate adrenergic function in the pathogenesis of hypertension In the presence of sensitized vessels or a limited ability to inactivate norepinephrine even normal sympathetic outflow might lead to increased vasoconstrictor activity Though little present evidence exists to indicate an abnormality of norepinephrine metabolism in hypertension a number of studies suggest that vascular reactivity to catecholamines may be increased Future insight into these important areas may do much to clarify the underlying role of sympathetic mechanisms in primary hypertension

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Diagnosis of Renal Hypertension

HARRIET P DUSTAN and EUGENE F POUTASSE

Research Division Cleveland Clinic Foundation

Renal hypertension is the most frequent of the secondary hypertensions which we now recognize A variety of renal lesions may be associated with hypertension These may be arterial parenchymal or perinephric in type they may be unilateral or bilateral in distribution and they may occur singly or in combination The arterial lesions which here concern us occur in the main renal arteries or their major branches all cause some encroachment on the arterial lumen In our experience most have been arteriosclerotic plaques (in a few cases associated with dissecting aneurysms) a smaller proportion have been characterized by fibrous intimal proliferation The most frequent of the parenchymal diseases are glomerulonephritis and pyelonephritis in the latter important disparities of renal size and function can occur The perinephric lesions which we have seen were perirenal hematomas in two adolescent males incident to football injuries Recognition of the type distribution and occurrence of renal lesions is important since in the case of unilateral renal disease the hypertension may remit following the appropriate renal surgery

The important radiographic techniques in the differential diagnosis of the renal hypertensions are intravenous urography retrograde pyelography and renal angiography Most of the patients with renal arterial disease whom we have studied have had urographic abnormalities In some the urograms have shown only slight disparities in renal length on one side or lesser concentrations of dye in the five minute films However these minor changes have been exceptional the general rule has been to find obvious differences in renal size and function Usually pyelonephritis leads to a structural abnormality that can be detected on the excretory urogram However it should be emphasized that normal urographic findings do not exclude the possibility of renal arterial disease nor pyelonephritis Thus intravenous urography can indicate the presence and in some cases the type of renal disease If the urogram does not outline the pelvo-calyceal system well retrograde pyelography gives important information in the differential diagnosis of pyelonephritis and occlusive arterial disease In the former case calyceal clubbing is the rule while in the latter there is calyceal atrophy At the present time renal angiography is the only method for demonstrating disease of the main renal arteries or their major branches It should be

employed as a routine diagnostic measure whenever such lesions are suspected. These three radiographic techniques can demonstrate the type, distribution and occurrence of renal lesions. This is the limit of their helpfulness for, as concerns unilateral renal disease, they cannot predict whether removal of a kidney or repair of an abnormal artery will result in lowering of blood pressure.

Recently Connor, Berthrong, Thomas and Howard have suggested a test diagnostic for unilateral renal disease responsible for hypertension.[1] This test involves the comparative analyses of urine specimens collected simultaneously from each kidney. The test was suggested by the findings in four hypertensive patients with unilateral renal disease whose hypertension remitted following nephrectomy. In each patient the affected kidney excreted urine of smaller volume and lower sodium concentration than its mate. Such prognostic precision in one test would eliminate the need for the diagnostic radiographic techniques usually employed in the diagnosis of renal hypertension.

TABLE 1 MEAN VALUES FOR RENAL FUNCTIONS OF THE INDIVIDUAL KIDNEYS IN HYPERTENSIVE PATIENTS

DIAGNOSIS	NO PATIENTS	VOLUME ml/min/1 73 M 1	2	GFR 3	4	U_{Na} mEq/L 5	6	U_{Osm} mOsm/L 7	8
Essential hypertension	10	3 83	3 80	42	44	60	62	377	375
Pyelonephritis	6	8 12	2.26	60	17	84	86	392	370
Unilateral arterial lesion	7	6 55	1 98	72	38	71	35	411	478
Bilateral arterial lesions	7	5 24	1 78	53	34	See Text			
Branch arterial lesion	5	7 66	4 15	76	38	75	75	381	380

Numbers appearing in odd numbered columns (1 3 5 7) are mean values for left kidneys and those in even numbered columns (2 4 6 8) are mean values for right kidneys.
** Values appearing in the even numbered columns (2 4 6 8) represent those of the affected or more affected kidney.

The purpose of this report is to describe the diagnostic and prognostic value of function tests of the individual kidneys of hypertensive patients with pyelonephritis or occlusive renal arterial lesions and to compare the renal functional characteristics with those found in patients with essential hypertension. In each patient the presence or absence of renal arterial disease had been established by renal angiography.

The function tests were performed during mannitol diuresis and Pitressin infusion. These conditions assure an adequate rate of urine flow, tend to stabilize electrolyte excretions and allow the measurement of "free" water reabsorption. The urine was collected simultaneously and quantitatively from each ureter over two 15-minute periods by a method previously described.[2] The functions here reported are urine flow (V), glomerular filtration rate (GFR), urine sodium concentration (U_{Na}) and urine osmolality (U_{Osm}). Analytical procedures used were those previously described.[3]

In Table I appear mean values for these renal functions in patients in various diagnostic groups—essential hypertension, pyelonephritis, unilateral and bilateral renal arterial disease. In ten patients with essential hypertension the functions were bilaterally equal: urine flow was practically the

same on each side as were glomerular filtration rate urine sodium concentration and osmolality Minor differences between the two sides were found The greatest depression in urine flow that was observed was 0 4 ml /min /1 73 M representing a 10 per cent reduction as compared to the opposite side Filtration rates were likewise similar and in only one patient was a depression as great as 14 per cent found Urine sodium concentration of the two sides was practically the same and in only one patient was a 16 per cent reduction observed Urine osmolality varied less than 7 per cent These results confirm the earlier findings of Chasis and Redisch that nephrosclerotic damage proceeds at the same rate in each kidney[4]

There were six patients with pyelonephritis all had disparities of renal size and function In each patient urine flow was less on the more affected side and this reflected a decrease in filtration rate urine sodium concentration was the same on the two sides urine osmolality tended to be less on the side of the lower urine flow

We have studied seven patients with a lesion in one main renal artery In each the affected kidney put out a smaller volume of urine not only because of the lower filtration rate but also because of the tendency toward increased water reabsorption as shown by increased urine osmolality Urine sodium concentration was strikingly depressed on the affected side and in each patient the value on that side was at least 20 per cent less than on the normal side and usually was of the order of 40 per cent less These results are similar to those observed in dogs with partial occlusion in one renal artery[5, 6] From these values alone it is impossible to state whether the low sodium concentration and high osmolality are the final expression of the relative decrease of filtration rate in an otherwise normal tubule resulting in a "glomerular tubular imbalance such as is thought to occur in acute glomerular nephritis

Of the 70 hypertensive patients whom we have found to have occlusive arterial disease 17 have had bilateral lesions The diagnosis of this type of renal hypertension is impossible without renal angiography since the results of function tests are too variable to be diagnostic In each of the seven patients in whom function tests were performed disparities of urine flow between the two sides were found which reflected proportional differences in filtration rate Values for urine sodium concentration and osmolality were widely variable and were not proportional to changes in urine flow and filtration rate Therefore mean values for these two functions do not appear in Table 1 as they would have no significance In three patients the urine sodium concentration was higher on the side of lower urine flow and filtration rate In another three the urine sodium concentration was lower and osmolality higher on the side of the lower urine flow and filtration rate suggesting a unilateral arterial lesion while in one patient urine sodium concentrations were identical on the two sides These results suggest that there are factors other than filtration rate that determine the urine sodium concentration and osmolality It is possible that the level of the intrarenal arterial pressure and the functional integrity of the tubular cells are important determinants of sodium and water reabsorption Thus it is apparent that tests of renal functions cannot give definitive information concerning the distribution of arterial lesions

An important group of renal hypertensives are those patients having occlusive disease in major branches of the renal artery These branch lesions

employed as a routine diagnostic measure whenever such lesions are suspected These three radiographic techniques can demonstrate the type distribution and occurrence of renal lesions This is the limit of their helpfulness for as concerns unilateral renal disease they cannot predict whether removal of a kidney or repair of an abnormal artery will result in lowering of blood pressure

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Discussion

Arthur Grollman *Moderator*

A C Corcoran	Milton Mendlowitz
J Richard Crout	George R Meneely
Harriet Dustan	Henry Schroeder
Robert Gaunt	Marvin Seven
Harry Goldblatt	Albert Sjoerdsma
Phyllis Hartroft	George Wakerlin
G M C Masson	Benjamin Zweifach

Dr Grollman Inasmuch as hypertension is a cardiovascular disturbance let us begin with a discussion of the relation of vascular changes to this disease There are two aspects to this problem In the first place what role do vascular changes in the kidney play in initiating hypertension? Secondly once the disease is established what does it do to the blood vessels? Dr Goldblatt will you discuss these points?

Dr Goldblatt I m delighted Dr Grollman to have this opportunity to give my views on this point because if you will refer to paragraph 3 of the brochure describing this symposium it states that information will be presented which indicates that vascular changes and consequently the symptoms of hypertension are probably a direct result of the blood pressure elevation But of course there s where I take issue immediately and I can say unequivocally that my views are just exactly the opposite of that statement It should be obvious that our view would have to be the opposite Never under any circumstances would I have thought of constricting a main renal artery in the hope of producing hypertension if I had thought that the hypertension comes first and the vascular disease second As a matter of fact the vascular disease is of no great consequence unless it involves the kidneys and therefore we tried to reproduce intrarenal arteriolar sclerosis which is so commonly found at autopsy in patients with essential hypertension Not being able to do that we retreated to the main renal artery and tried to reproduce the intrarenal hemodynamic disturbance which probably occurs in the kidney s vascular disease by constricting the main renal artery There are several points to make One the mere fact that the blood pressure did become elevated as a result of this procedure is of great significance More than that of course is the fact that in some animals like the rat goat and sheep the blood pressure may remain elevated for a considerable time This sort of thing may happen even in human beings If you just take out the kidney of such an animal the blood pressure falls and fortunately in man (we have records of more than 500 now) the blood pressure has fallen to normal as a result of removal of a single diseased kidney Under no conditions can you explain that kind of effect on the basis that the hypertension comes first on the basis that it is endocrinogenic neurogenic psychoneurogenic or anything else because why in the world would the blood

pressure fall to normal when the kidney is removed? It would take me about an hour to try to convince you with more of the evidence but those two things it seems to me are incontrovertible evidence that the vascular disease which we see in essential hypertension is something which comes first Only when and if it involves the kidney does the blood pressure fall following nephrectomy Now the mere fact that it doesn t fall in all cases in which a *single kidney is removed is merely an indication of inadequacy of the meth ods of studying these kidneys* We cannot tell from most of the studies that we have made whether there is a disturbance of renal excretory function in a kidney that is also the seat of vascular disease Therefore in all probability in those in which it fails the opposite kidney is diseased

Dr Grollman Thank you Dr Goldblatt I do not believe that this is the unanimous opinion of all the panel Is there any member of the panel who would like to take issue with Dr Goldblatt?

Dr Schroeder Dr Goldblatt knows what I am going to say just as I knew what he was going to say Some years ago we did some experiments in the dog A few selected dogs will get as you said an elevated blood pressure when the artery of only one kidney is clamped Then we did biop sies at about yearly intervals on the other kidney We also took some dogs and cut their carotid sinus and aortic depressor nerves to give them neuro genic hypertension—which I might say was a terrific hypertension—and we did serial biopsies on the kidneys of those dogs Dr Gustave Dammon who is now at Peter Bent Brigham Hospital examined the sections The first change in the kidney occurred about two years after the hypertension was established The first change was not in the arteriole but in the glomerulus There was thickening of the basal membrane of the glomerular capsule and a certain amount of infiltration of PAS staining material in the glomerular tuft At two years Dr Dammon could not convince himself that there was any change in the arterioles but at four years there was definite change beginning and at seven years there was a change that was quite obvious When the slides were then re examined you could see the changes were be ginning at about two years in the arteriole Thats in the dog I think in the rat of course if you do something to one kidney you get disease in the other kidney quite consistently You can take out the kidney that you clamped in the rat and still maintain the hypertension I don t know which comes first but it seems to me that in most cases we did see this thing develop later after the hypertension was well established

Dr Grollman Anyone else care to discuss this point?

Dr Zweifach I d just like to ask Dr Schroeder whether or not he is merely using the tools of the pathologist to indicate that this particular kidney is abnormal Are you assuming because you can t see that the vascu lar tree in this particular kidney is abnormal that it is not abnormal? May this not be a biochemical or a functional change which eventually will show up as pathology? I don t think we can rule out the sequence here on the basis of pathological inspection

Dr. Schroeder Like Dr Grollman I believe that there is a biochemical change quite early in experimental renal hypertension

DR GROLLMAN We are considering now visible arterial changes Those are the ones that Dr Goldblatt and Dr Schroeder have in mind Is a primary lesion in the renal blood vessel responsible for hypertension or are the vascular lesions observed at autopsy the result of pre existing long standing hypertention?

DR GOLDBLATT I m going to take advantage of the opportunity to say just a few more words especially in answer to my good friend Harry Schroeder I have studied dogs for even longer periods than Dr Schroeder and I think I know diseased blood vessels when I see them I personally must say that I have never yet seen anything remotely resembling arteriolar sclerosis or indeed arteriosclerosis of the larger blood vessels or arteriosclerosis of the aorta in animals that have had hypertension for a great many years eight and a half years is my longest period I have studied this point with the greatest of care and although it is even in print that we were the first to produce arteriolar sclerosis as a result of hypertension there is nothing farther from the truth than that Actually what has been referred to as arteriolar sclerosis is hypertrophy and hyperplasia of the media and not simple intimal arteriolar sclerosis or arteriosclerosis I would like more than anything else to have an opportunity to examine those sections of Schroeder s to satisfy myself that what he has just said is actually correct One thing we cannot deny and that is that an occasional animal might have developed such a condition but to go as far as Schroeder has on the basis of those observations of Dammon I am afraid is just a little too much

DR. SCHROEDER Dr Goldblatt could I mention the names of Castleman and Smithwick? They took little smidgens as you remember out of one kidney at sympathectomy and found that in half of the cases in which the hypertension was serious enough in their judgment to have a lumbar dorsal sympathectomy there was little or no vascular disease When the criticism was made that this was only a unilateral biopsy they did 100 bilateral biopsies and found the difference in vascular disease between the two sides to be minimal If you can get hypertension badly enough in Dr Smithwick s estimation to be operated on and still have no vascular disease in half the cases hypertension doesn t start with a clamp

DR GOLDBLATT I m afraid Dr Schroeder that you are not quite up to date on the figures even of Castleman and Smithwick because in recent times they have admitted that their earlier figures were really low Actually there was some change in 90 per cent But they ve divided those 90 per cent into slight moderate and severe and the severe is around 50 per cent That s just wonderful so far as I m concerned The fact is that I have had an opportunity to examine small pieces of kidney and it s quite remarkable how few arterioles and especially preglomerular arterioles you come across in such specimens—sometimes none sometimes one sometimes up to five and then you have reached just about the limit Imagine there are a million pre glomerular arterioles in every kidney Now examine three to five and see what the probability is that you might miss the relation especially when arteriolar sclerosis is what we call a beaded process One part of an arteriole may be perfectly normal and several microns from that disease may be found And so you see how dangerous statistically such a study is I m

delighted with the figures of Castleman and Smithwick because there is as much disease as there is in the kidneys of individuals with hypertension and in whom they feel they can reverse the process In other words those patients are not cases of most advanced hypertension who were terminal The pathologist finds it in virtually 100 per cent of the cases that are at the end of the disease but even in the middle stage of the disease the incidence is very high

DR GROLLMAN I regret to stop this animated discussion but we must pass to other important aspects of the problem

DR WAKERLIN May I make a comment Dr Grollman? I think it might be pointed out that the dog is more resistant to the arteriosclerotic effects of hypertension than undoubtedly is man or than is the rat Even the dog however does respond to certain effects of hypertension in relation to the vessels as is demonstrated by the fact that the renal hypertensive dog develops a greater degree of experimental cholesterol atherosclerosis than does the normotensive dog so that this is a relative rather than an absolute difference

DR GROLLMAN Thank you, Dr Wakerlin Perhaps we might summarize by asking the panel for an expression of their opinion However let us limit ourselves to essential hypertension excluding periarteritis and other obvious vascular diseases How many members of this panel in addition to Dr Goldblatt feel that the renal vascular disturbance is primary and that the hypertension then follows as a result of the renal vascular disease?

DR. MASSON I'm not sure that I understand you I believe there is a biochemical lesion

DR GROLLMAN We are speaking here of microscopically visible vascular lesions as described by Dr Goldblatt Does primary hypertension result from such lesions?

The majority of the panel apparently do not share Dr Goldblatt's view on this question Let us now proceed to another aspect of this problem namely the heart Dr Wakerlin do you think that there is a specific lesion in the heart which gives rise to cardiac failure in two-thirds of all patients with hypertension or is this failure of the heart and its hypertrophy merely a consequence of increased mechanical work?

DR WAKERLIN I think it's generally thought that the latter is the case that it is the result of the increased mechanical work that the heart must do But I think it is entirely possible that here there may be an intrinsic effect on the heart And one of the reasons that I think so is that there are some small suggestive evidences that perhaps very early in essential hypertension there may be an increase in cardiac output which then is compensated for by the increase in peripheral vasoconstriction If this should turn out to be the case and I think we need some studies of patients with early essential hypertension to rule this in or out then the heart would play a much more basic role in the production of the hypertension than at present we conceive it to be I recall some studies done on patients with hypertension due to acute glomerulonephritis in whom it was found (in a small series) that the

first thing that happened was an increase in cardiac output without any great amount of increase in peripheral resistance If this should turn out to be so for patients with very early essential hypertension it would be quite important We have recently produced experimental hypertension by constricting the carotid sinus area and in some of these dogs we found that very early in the hypertension there was no increased peripheral resistance but there was an increase in cardiac output which over a period of several months disappeared as the peripheral resistance increased So I think it is possible that the heart may play a primary rather than a secondary role in hypertension perhaps even in essential hypertension We know of course that angiotonin has a cardiotonic effect on the myocardium It increases the tonus and the contractility of heart muscle as Andrews showed with renin some years ago and as others have shown since

Dr Crout Dr Grollman I'd like to ask Dr Wakerlin to straighten me out on a point that has always puzzled me If I correctly grasp the control of the cardiac output it responds to tissue demand and that tissue demand is also reflected by the adjustment of the arterioles The point that puzzles me is why the baroreceptors permit the development of hypertension?

Dr Wakerlin I think the best evidence we have on that point is that produced by McCubbin and his group which suggests that the baroreceptors in some way adjust to this situation The question of course is why they adjust and I think that is something that remains to be determined It seems to be an adjustment of the peripheral receptors rather than central changes Just why this happens I don't think we know There must be some sort of biochemical lesion in these receptors because there doesn't seem to be any change in their structure

Dr Meneely You know the concept expressed in "Science Is a Sacred Cow" that the important thing in science is a common factor I think we ought to look for things that are constantly present in hypertension The whole pressure control mechanism has to acquiesce in hypertension hasn't it?

Dr Wakerlin There is no question about that It operates but it operates on a higher base and the question is what brings this about? The whole buffer nerve mechanism operates at a higher base I think we need some studies here again in patients with incipient essential hypertension to see what the situation is Perhaps it may be similar to what it is in McCubbin's dog

Dr Grollman An important aspect of the subject that I think ought to be discussed is the fact that many believe that hypertension is an inheritable disease Although we have to do experiments to establish many fundamental points that we cannot settle by clinical observation nevertheless clinical observation does give us many starting points which we cannot perceive in the animal One of these is the question of heredity Hypertension seems to be a purely human disease it rarely occurs in other animals except in the presence of obvious renal lesions In the human where it is hereditary when does it start? If it's inherited it begins in the genes at the time of conception That being the case when the individual is born and when the pressure is

still normal in childhood that individual really has incipient hypertension What about this congenital origin of hypertension Dr Mendlowitz?

DR MENDLOWITZ I don t think there is very much question in the minds of most investigators that essential hypertension is an inherited disease I think this has been shown quite clearly in many studies The question in my mind has always been how is this hereditary factor transmitted? Dr Grollman pointed out that hypertension doesn t appear until later on in life and with the implied question of how that could be hereditary It seems to me that there need not be such a question After all many inherited diseases—gout for example or diabetes—appear later on in life The tendency may be there or the trait may be there and even pathologic function may be there long before hypertension as such appears

We in our studies have been led to conclusions that Dr Crout emphasized namely that sympathetic function is not increased in hypertension but that reactivity to normal sympathetic tone is

It seems to me that Goldblatt and others who implicate the renal mechanism in hypertension must tell us first how arteriolosclerosis in the kidney appears in the first place in order to constrict these blood vessels Are we to divorce function from anatomy entirely or is it possible that constriction of these blood vessels through functional mechanisms eventually produces the arteriolar sclerosis and then adds a renal and an arteriolosclerotic mechanism to the disease as it progresses?

DR GROLLMAN Dr Meneely do you want to express an opinion about the origin of essential hypertension?

DR MENEELY The only point that I would like to make is that it does seem to us that no matter what else you are going to do you ve got to supply some salt I d like very much to hear from Dr Goldblatt where he feels the initiation of the hypertension observed in high salt eating or high salt water drinking animals occurs We can t find any anatomical lesions by ordinary histologic methods in the vessels of our mildly or moderately hypertensive animals after a year or even after two years This is not using special stains or anything of that sort, but just ordinary conventional techniques

DR. GOLDBLATT I am delighted to have the opportunity to speak again on this particular subject because what Dr Meneely has just said falls right in line with what I said a little while ago Never under any circumstances have I said that there is no such thing as a functional element in elevation of blood pressure Nor have I denied that there is such a thing as a psychoneurogenic type of hypertension I certainly have never denied that there can be such a thing as an endocrinogenic type of hypertension One would be pretty daring to say that a pheochromocytoma associated with hypertension is not the cause of the elevation of blood pressure when just removing the tumor cures the elevation of blood pressure That s obvious What I have said also is that there are individuals who whether by heredity or otherwise have a system which responds unusually to normal stimuli and neurogenic or psychoneurogenic stimuli may be a part of so called essential hypertension As a matter of fact it is my own belief that the doctor treats that modicum of the hypertension or the elevation of blood pressure that

occurs in practically all cases of hypertension When a man gives assurance or raspberry juice to a patient the blood pressure begins to go down The patient gets accustomed to him and the blood pressure falls It never falls to normal certainly not as a result of the raspberry juice but there is a change Now the doctor if he is not too critical says Well I have lowered your blood pressure I think that the *patient* has lowered his blood pressure in most cases His stimuli whatever they are that have been adding that modicum of elevation of blood pressure have either vanished or he has become insensitive to them So far as I m concerned when it comes to the matter of heredity I believe that what were inheriting is our rubber our vascular bed I think back upon a boy of 13 years of age with hypertension who went on to his death from apoplexy and who had the most profound vascular disease particularly limited to the kidneys of any individual I have ever seen young or old That little boy probably inherited his poor rubber from his parents

DR. GROLLMAN We all speak of increased peripheral resistance as one of the hemodynamic features of hypertension like so many other things in medicine we speak of it but we can t see it How do you visualize this increased peripheral resistance? What exactly happens in the vessels Dr Zweifach?

DR. ZWEIFACH I think the central theme here always keeps coming back to the effector unit the smooth muscle cell in the small blood vessel This presumably is responsible by its activity for altering the peripheral resistance and thereby elevating the blood pressure We ve heard talk of more or less mechanical factors whereby changes in the wall can give rise to this and we have alluded to the possibility that there s no reason to presuppose that functional biochemical factors can t alter the status of the smooth muscle cell I think I would put in that category the whole problem of salt metabolism since we know that electrolytes of this kind (sodium depletion and sodium excess and potassium exchanges) influence reactivity tremendously and the capacity of the small blood vessels not only to respond but once responding to relax and reconstitute themselves for receiving a second stimulus It may very well be that what we really should consider to be a basic mechanism is some sort of electrolyte shift But there must be a whole chain of events which ultimately leads to this We are talking about peripheral resistance just as we talked yesterday about blood flow to organs I think this is somewhat misleading in that we are apt to assume that peripheral resistance is increased because the arterioles are comparably narrowed in all parts of the body We know this is not so And the same holds true if we are measuring blood flow through an organ If we say that a clamp on the renal artery does or does not reduce the blood flow through the kidney this does not mean that there is not a redistribution of flow within the kidney and this is certainly true for other organs So that I think that one must in talking about vascular reactivity not only refer to particular portions of a vascular tree but to particular organ systems And this brings me to a point that I will raise later this morning that in casting about for the *modus operandi* here there have been suggestions in the literature that there is circulating a humoral agent whether it be a positive or an inhibitory factor doesn t matter But then we suppose that this humoral agent does the same

thing to all blood vessels and this is not true Any humoral agent whether it is noradrenalin adrenalin renin angiotonin or any of these compounds that one can introduce into the circulation has different effects on different vascular beds Indeed they may have opposite effects on different vascular beds There again we must very carefully evaluate what we are talking about in terms of etiology I think we may very well find that the predisposing factor which alters vascular reactivity is inherent in the particular organ where this vascular change develops But most of the local intrinsic mechanisms for regulating blood flow within that organ reside within the parenchyma of that tissue itself

Dr Grollman Dr Gaunt do you feel that the adrenal both medulla and cortex plays any role at all in the initiation of essential hypertension? We obviously must accept aldosteronism and pheochromocytoma as rare causes of hypertension

Dr Gaunt I ll try to talk a little more about it this afternoon but I m certainly in agreement with what I think was the tenor of the remark you just made that we must consider the possible role of aldosterone and that sort of thing in hypertension It is certainly a possibility that it can be a contributing factor under certain conditions but we have not nailed down that fact or nailed down the conditions under which it may occur Until this can be definitely demonstrated by more convincing evidence than we have seen yet I think it s much safer just to look on the adrenocortical hormones as possible accessory factors in these more common types of hypertension than to go overboard in assigning them a critical role

Dr Grollman Dr Hartroft you feel that the juxtaglomerular zone has something to do with hypertension Would you summarize what part you think it plays or how it functions in hypertension? Is it overactivity underactivity or don t we know?

Dr Hartroft Dr Grollman were not really looking for the cause of hypertension but were trying to find out how juxtaglomerular cells function and we really believe that they are more basically related to electrolyte metabolism than to hypertension per se But it is certainly possible that they may become involved in the pathogenesis of hypertension The most interesting change I think is in unilateral renal hypertension in the rat in which they respond quite differently and in opposite directions in the two kidneys

Dr Grollman Dr Crout I took it from your discussion this morning that you don t feel there is any definite evidence that catecholamine plays any part in the pathogenesis of hypertension Do you think it very probable that change in reactivity of the autonomic nervous system is involved?

Dr Crout There is no evidence at all that the production of norepinephrine is increased I think this is clear in that a number of people have tried to explain away catecholamine data but this should not be done No I think that the sympathetic transmitter may participate in the hypertensive process but if it participates in the hypertensive process more than it participates in the regulation of normal arteriolar tone this requires a more sensitive vessel because there isn t any more of it in hypertension

DR GROLLMAN Dr Dustan I'm sure members of the audience will be interested to know how often they will find the renal arterial lesions of which you have spoken That is of great practical importance We always wonder whether we are overlooking a patient with a lesion that can be cured Therefore Dr Dustan tell us how frequently the general practitioner who sees the patient with hypertension will encounter one of these unilateral curable vascular lesions Secondly in those in whom this unilateral lesion is corrected operatively what percentage will actually have a permanent cure and not a temporary decline in blood pressure?

DR DUSTAN Dr Grollman I think that the type of nephrectomy or partial nephrectomy that is done in Cleveland must be very extra special because of this group of patients who have been operated on in 75 per cent there has been remission of diastolic hypertension and in none of them has hypertension recurred Now I grant you that this represents a group of patients who have been followed for only six months to three years and this is too short a time in which to say that hypertension has remitted forever Atherosclerotic plaques are the most frequent cause of the occlusive renal arterial lesion If these atherosclerotic plaques developed in one renal artery I see no reason why they couldn't develop in another renal artery or in the coronary circulation or in the cerebral circulation Therefore it is possible that patients develop atherosclerosis of the remaining renal artery—what percentage of patients I don't know As to the frequency of this phenomenon all I know is that it's amazing how many you find if you look But naturally one is not going to look in every hypertensive patient We have found them in 25 per cent of the patients in whom we have performed angiography I don't know what percentage over all

DR GROLLMAN Dr Schroeder would you like to add to this subject from your wide clinical experience?

DR SCHROEDER I think we have two patients now out of 300 originally before World War II who have sustained a normal blood pressure after nephrectomy One had an atrophic pyelonephritis and the other had marked hydronephrosis It had been my impression before the use of angiography that we could help about half of 1 per cent of hypertensives by nephrectomy It was also a strong clinical impression of course based on experimental data in animals that the longer you had your hypertension due to unilateral renal disease the less likely you were to get a cure because of the development of nephrosclerosis in the opposite kidney if man is like the rat Now that may or may not be so A third point is that you often get fooled by finding bilateral disease at autopsy after you've done a unilateral nephrectomy which is what you usually do in man You find as we have found several times an occlusive plaque in the opposite renal artery of the type that Dr Goldblatt is concerned with and which presumably is the cause of the hypertension I'd like to make one comment though and that is that I don't advise anybody to do retrograde pyelograms indiscriminately in every hypertensive We have lost several patients from coronary occlusion or cerebral vascular accidents occurring shortly after the retrograde pyelogram It is a stressful procedure and sometimes painful If a retrograde pyelogram has to be done because of nonvisualization with the intravenous

pyelogram I would suggest that one side be done at a time particularly in people with impairment of renal function because sometimes you get renal shutdown or you get uremia

Dr Goldblatt May I say a word Dr Grollman on this subject? If there ever was a skeptic about the relationship of unilateral renal disease to hypertension and especially about the probability of lowering the blood pressure as the result of removal of a kidney it was Homer Smith Yet Homer Smith not more than a year and a half ago published a careful review of the whole subject up to that time and he analyzed the results of operations in 575 patients So far as I know he was the first ever to use the word cure of essential hypertension as a result of the removal of the one and only diseased kidney Obviously that s about 26 per cent and that s good because as we have stated over and over again here it is impossible to know the state of the other kidney I would like to see documented cases Dr Grollman that come back with hypertension An occasional one might and there is no reason why they shouldn t because as Dr Dustan said they might have a modicum of vascular disease in the other kidney at the time of the operation not sufficient to play an important part in the elevation of blood pressure but it may become more manifest later on There is no reason under the sun why such patients should not go on to the redevelopment of hypertension

Monamine Oxidase and Hypertension*

HENRY A SCHROEDER

Dartmouth Medical School and Brattleboro Retreat

THEORY

The relationship of the enzyme monamine oxidase to the generalized vasospasm encountered in chronic arterial hypertension has received some theoretical discussion off and on during the past twenty years but no definitive evidence has been discovered to implicate the enzyme directly Holtz Credner and Walter were the first to theorize that some disturbance in enzyme activity might be related to the pathogenesis of hypertension demonstrating that renal decarboxylation of certain amino acids would lead to the excessive production of vasoactive primary amines if monamine oxidase activity were at the same time depressed [1]

Bing and Zucker demonstrated that hypoxic kidney *in vivo* would decarboxylate dihydroxyphenylalanine and liberate hydroxytyramine which in normal kidney was oxidized while we found that the amino acid was pressor in rats [2] Since both decarboxylases and monamine oxidase occur in most mammalian kidneys (the latter is not found in rat kidney), and since decarboxylases are anaerobic enzymes removing carboxyl groups from some

* Prepared under a grant in aid from the American Heart Association

amino acids while the oxidases are aerobic it seemed possible that reduction of renal oxygen tension would lead to diminished deamination of primary amine *in situ* but would not affect the normal rate of decarboxylation This theory appeared to be especially attractive when Kohn demonstrated linear sensitivity of monamine oxidase to oxygen tension *in vitro* a 50 per cent reduction in oxygen tension resulting in halving the activity of the enzyme[4] Therefore by 1938 the case for a disturbance in renal primary amine metabolism in hypertension was on a sound but indirect theoretical basis on *in vitro* studies only Although there is much additional indirect evidence from later studies *in vitro* and *in vivo* the case still remains an attractive though hypothetical one so far unconfirmed by exact measurements in man

Renal biochemists have been loath to accept the alternate pathway" of amino acid catabolism through decarboxylation and amine oxidation And yet amine oxidation provides an excellent source of ammonia and decarboxylation of bicarbonate The fact that only 40 to 60 per cent of normal urinary ammonia comes from glutamine leaves one with the question of where the rest arises Mammalian kidney has little l amino acid oxidase other than glycine oxidase and much decarboxylase and amine oxidase An examination of this alternate pathway with a study of those amino acids whose amines are vasoactive and are therefore capable of deamination by monamine oxidase is in urgent order

THE ENZYME

Monamine oxidase first discovered and described by Blaschko Richter and Schlossmann is an oxidase or a group of oxidases having specificity for terminal NH of 15 primary amines resulting from the decarboxylation of 12 naturally occurring amino acids The reaction causes oxidation of the amine side chains to aldehydes most of which are unstable with the liberation of ammonia By a curious coincidence most if not all of these primary amines show vasoactivity

The amino acid precursors and the vasoactive primary amines resulting theoretically from their decarboxylation are dihydroxyphenylalanine hydroxytyramine leucine isoamylamine tyrosine tyramine tryptophane tryptamine 5 hydroxytryptophane serotonin norvaline butylamine norleucine amylamine phenylalanine phenylethylamine isoleucine β methylbutyl amine serine ethanolamine threonine β hydroxypropylamine and dihydroxyphenylserine l norepinephrine[6] Renal mammalian decarboxylases for only five of these amino acids have been discovered tyrosine leucine tryptophane 5 hydroxytryptophane and dihydroxyphenylalanine although bacterial enzymes for more are known To my knowledge systematic search for renal decarboxylases from this viewpoint has not been done Those analyzed have so far required zinc and pyridoxal as cofactors

Monamine oxidase preparations also oxidize the secondary amine nitrogen of l epinephrine and probably the nitrogen of the amines coming from 3 5 diiodotyrosine and thyroxine Unnatural (d) forms are weakly oxidized They do not affect diamines such as histamine and cadaverine which are oxidized by diamine oxidase or histaminase the decarboxylase precursors of which are known The only natural pressor amine not oxidized is guanidine *

For a thorough discussion of what is known about the enzyme to date the reader is referred to the recent impartial and excellent review by Davison[20]

Little is known of the cofactors of guinea pig or rat monamine oxidase Indirect experiments *in vivo* with a number of trace metals show no specific regressive inhibition with decreasing concentrations to 0 1 millimolar metal (10^{-4}) by Mg^{++} Ti^{+++} Ti^{4+} Cr^{++} Cr^{+++} Mn^{++} Fe^{++} Fe^{+++} Ni^{++} Cu^{+} Cu^{++} Zn^{++} Cd^{++} Hg^{++} and UO_2^{--} At concentrations of 10^{-5} however there is some stimulation of activity by Co^{++} and marked stimulation by V^{+++} more by V^{4+} and none by V^{5+} At concentrations of 10^{-} there is inhibition only by Cu^{++} and Hg^{++} probably a nonspecific effect[7] Thus there is no evidence by the laws of chelation for the existence of any of the known essential metals as cofactors (as in the case of two carboxylases where Cd^{++} appears a specific displacer of Zn^{++}) but there is some suggestion that a tetravalent trivalent vanadium system may be a cofactor*

Several inhibitors of the guinea pig enzyme are known and a current theory involving cerebral metabolism by monamine oxidase and disturbed mental states uses inhibitors therapeutically this theory is as tenable as the one concerned with hypertension These inhibitors are all hydrazine or closely allied derivatives[8] (see paper on *Pharmacology of Hydralazine*) They include iproniazid (10^{-3}) as first discovered by Zeller and Barsky[9] 1 4 dihydrazinopyridazine (10^{-3}) phthalazine (10^{-5}) 1 hydrazinoisoquinoline (10^{-})[8] 2 hydrazino quinoline (10^{-3}) and benzoquinone guanylhydrazone allylthiosemicarbazone (10^{-3})[10]

In our hands only two organic stimulators are known 1 hydrazino phthalazine and 1 4 dihydrazinophthalazine which have a definite effect at 10^{-4} concentrations At heavy (10^{-}) concentrations sodium nitroprusside and β mercaptopropionic acid appear to stimulate the enzyme[8] Others in Europe have not found stimulation with these two hydrazines but slight and inconstant inhibition which varies with the season[10] differences in guinea pigs may be responsible The effect of stimulators upon the human renal enzyme remains to be studied

RELATION TO HYPERTENSION *IN VITRO* EFFECTS

The vasoactive polypeptide *hypertensin is inactivated by the enzyme* as first discovered in our laboratory[11] and confirmed by Croxatto and Croxatto[1] with a concurrent oxygen uptake The uptake is first rapid and then slow unlike that with tyramine which is a straight line function[13] The vasoactive and smooth muscle constrictor pherentasin procured from human hypertensive arterial blood is inactivated by the enzyme[14] It is quite possible that pherentasin and the various hypertensins obtained from animals are similar but not identical substances inactivation implies a terminal primary amine It is probable that such peptides maintain vasoconstriction through a nephrogenic mechanism and are the humoral agents responsible for a large component of severe hypertension But there is no evidence that tissue stores of the enzyme are disturbed in hypertension

* Stimulation of oxygen uptake in any impure enzyme preparation may be the result of metal effect on other oxidases not inhibited by the cyanide in the preparation Vanadium acts on some system dehydrogenating and oxidizing the fatty acid in phospholipid for example

RELATION TO HYPERTENSION IN VIVO EFFECTS

Many experiments were performed by us in 1940-41 on the direct effect of a preparation of monamine oxidase obtained from hog liver upon experimental renal hypertension[11] The enzyme made in large quantities by Merck and Co contained no other demonstrable enzymatic activity a large number of controls using inactivated enzyme altered by heat pH and chemicals were employed Injection (I V) into hypertensive rats of minute amounts of the active material resulted in a fall of blood pressure to normal levels the level of normotensive rats was less or not at all affected Prior injection caused inhibition of the pressor activity of renin in other words tachyphylaxis was immediately induced The pressor activity of hypertensin was strongly modified but not abolished[15] probably because monamine oxidase is a slowly acting enzyme and the hypertensin had time to act before being destroyed

Daily intravenous injection of the active material into hypertensive dogs caused a drop in pressure to normal levels lasting 24 hours or more When normal doses were given blood urea nitrogen fell when excessive doses caused marked hypotension the resultant severe renal ischemia caused by the inflexible clamps on the renal arteries resulted in anuria and uremic death[15] Inactivated enzyme produced no demonstrable effects although it was identical in composition with the active

No chronic changes were observed with feeding the enzyme in large quantities to rats dogs or man (except that the usual odor of human feces was abolished possibly partly because of some diamine oxidase present) Because the enzyme has not been purified to the point where it can be injected into human beings no experiments of this type have been done These results suggest that the enzyme is a powerful substance in neutralizing humoral nephrogenic hypertensive influences

Indirect evidence for some disturbance in renal amine metabolism is found in man by measuring the amount of primary amine in extracts of hypertensive arterial blood as compared to those of normotensive blood Two different biochemists one working before the war and one after reported similar results Stock found four of 16 normotensive extracts with no demonstrable primary amine four with 1γ six with 1 5 to 4γ and only two with 4 to 7γ per ml of blood in terms of isoamylamine (As a mixture of amines was present one substance was chosen as a reference) Of 42 hypertensive cases 13 contained more than 10γ (the limit of the method) seven from 4 to 10γ three contained none and the rest 1 to 4γ per ml[16] Although there was no clear cut distinction the majority of the hypertensive extracts contained much more than did the minority of the normotensives Unfortunately the highest normotensive values were from patients with congestive heart failure Olsen using a different standard found "elevated levels in three of 16 normotensive extracts 15 of 17 extracts from patients with severe hypertension and a large renal element 11 of 19 with neurogenic hypertension and three of four with malignant hypertension[17] His values were about ten times higher than Stock s because of the difference in standard but the distribution was similar The method does not measure phenolic or catecholic amines Thus most hypertensive patients appear to have elevated primary amine levels in their blood Few or no amines were

found in brachial venous blood, probably because they were oxidized by arterial smooth muscle Considerable amounts were found in renal venous blood in the six cases tested [1]

Presumably there is an inhibition of monamine oxidase activity in an organ with a large blood supply directly feeding into the circulation Kidneys or lungs appear the more obvious organs

Further evidence for abnormal amine metabolism in hypertension is given in the work of Davies Wolfe and Perry in our laboratories [18] They found some eight primary amines excreted in the urine of normotensive subjects with considerable variation from day to day Individual amines were excreted usually in amounts of 20 to 100 μg per day roughly 1 to 5 per cent of the amino acids excreted Hypertensive patients failed to excrete six of those found in normotensive urine and many tended to show amines not found in normal urine The amines were not identified No larger quantities were excreted by hypertensive subjects

EXAMINATION OF THE THEORY

The question must be answered Can these primary amines other than norepinephrine so regularly identified in blood and urine of hypertensive patients be responsible for the generalized vasospasm present in this disease?

The answer is probably No A careful evaluation of the pressor activities of each individual amine as determined by Dale and Barger fifty years ago reveals that enormous quantities would be required in blood in order to cause elevation of blood pressure Compared to norepinephrine the relative potencies of the amines listed elsewhere in this article vary from 1 2 to 0 06 per cent [6] Obviously amounts large enough to cause sustained vasoconstriction would constitute a sizable fraction of blood nonprotein nitrogen and would show in the urine

Another question is pertinent Can these amines cause other effects or symptoms found in hypertension? The answer is probably Yes From what is beginning to be understood of the role of primary amines in cerebral metabolism and nerve transmission it is entirely possible that much of the tension anxiety and nervousness exhibited by and complained of by hypertensive patients as well as the fast dysrhythmia so frequently seen in encephalograms in hypertensive patients could be the result of abnormal amine metabolism in kidney with humoral transport to brain [19] In that event hypertension has somatopsychic" rather than psychosomatic" components which as many of us have noticed disappear when the hypertension is controlled

If disturbances of monamine oxidase were directly concerned in hypertension as a causal phenomenon enzyme inhibitors should cause elevated blood pressure They do not Local inhibition however is consistent with the known experimental data

SUMMARY

Experimentally monamine oxidase is a potent antihypertensive substance in rats and dogs, rendering the former tachyphylactic to the action of renin and hypertensin and controlling renal hypertension in the latter It oxidizes both hypertensin and pherentasin *in vitro* and inactivates them *in vivo*

The monamine oxidase decarboxylase system in mammalian kidney represents an alternate pathway for amino acid catabolism and may be a source of urinary ammonia. Reduction of renal oxygen tension may cause reduction in monamine oxidase activity leading to increased amine levels in arterial blood

There is ample indirect evidence that a disturbance in primary amine metabolism is present in chronic arterial hypertension manifest by increased amine levels in blood and alterations in urine Presumably this disturbance involves a local partial inhibition of monamine oxidase activity in either kidney or less probably lung There is no evidence that this disturbance is more than a secondary manifestation of the hypertensive process responsible perhaps for some symptoms but not directly for generalized vasospasm

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Monoamine Oxidase Inhibitors

ALBERT SJOERDSMA

National Heart Institute National Institutes of Health

During the past few years a great deal of attention has been given to the possible roles of naturally occurring monoamines such as serotonin (5 hydroxytryptamine) and norepinephrine in the central nervous system Drug induced alterations in the metabolism of these amines have been shown to be associated with changes in central functions Relatively little consideration has been given however to physiologic events peripherally Our interest in this connection has centered on correlating changes in amine metabolism with alterations in the blood pressure of patients with primary hypertension

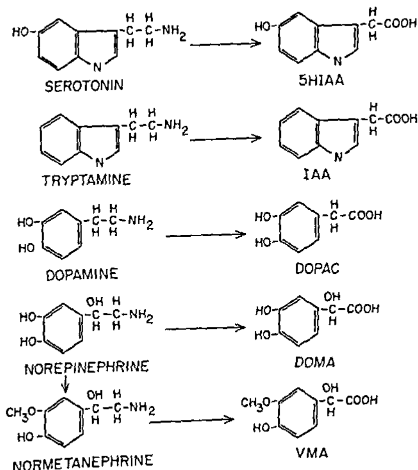


Fig 1 Some vasoactive amines and their MAO metabolites 5HIAA = 5-hydroxyindoleacetic acid IAA = indoleacetic acid DOPAC = 3 4 dihydroxyphenylacetic acid DOMA = 3 4-dihydroxymandelic acid VMA = 3 methoxy-4 hydroxymandelic acid

Oxidative deamination via the enzyme(s) monoamine oxidase (MAO) is an important means of inactivation for several vasoactive amines found in man. The structures of some of these amines and their MAO metabolites are shown in Figure 1. Drugs which could be shown to inhibit this enzyme in the human might be expected to produce alterations in blood pressure. It is of interest that isopropyl isonicotinyl hydrazine (iproniazid), a potent MAO inhibitor in animals which was first administered to patients several years ago as a tuberculostatic, has as one of its major side effects postural hypotension. A few attempts to make use of this effect of the drug in hypertensives have been only moderately successful.[2] Certain other MAO inhibitors also appear to have the property of lowering blood pressure in man.

There appeared to be two requirements for obtaining meaningful data concerning a possible relationship between MAO inhibition and changes in blood pressure: (1) that a method be developed to measure MAO inhibition in man and (2) that inhibitors of differing chemical structure be used in order that the effects of MAO inhibition might be separated from other biochemical and physiologic actions of the compounds. Another important aspect of this approach would be to ascertain whether drugs which appeared to be inhibitors in animal tissues *in vitro* and *in vivo* would have any significant enzymatic effect in man at tolerable clinical dosage.

MEASUREMENT OF MAO INHIBITION IN MAN

A simple test was devised based on the conversion of orally administered serotonin to 5 hydroxyindoleacetic acid, the urinary end product of MAO activity.[3] Although a diminution of 5HIAA production from orally administered serotonin might be indicative of an over all MAO inhibition with a particular drug, *it was felt that only the inhibition occurring in the gut* and possibly the liver was being measured by the test. Several experiments were done which confirm this probability and are described elsewhere.[4] Because of this shortcoming in the oral serotonin test, other approaches to measuring over all MAO inhibition have been explored. Preliminary observations by Oates and Sjoerdsma of this laboratory[5] indicate that the urinary excretion of tryptamine is a sensitive index of *over all MAO activity*, and measurements of this amine afford another method of evaluating MAO inhibition in man. From Figure 1 it is apparent that there are other similar

TABLE 1 EFFECT OF VARIOUS DRUGS ON MAO IN MAN AND IN VITRO

DRUGS	DOSE (mg)/interval	% INHIBITION OF SEROTONIN TO 5HIAA IN MAN	CONC PRODUCING APPROX 50% INHIBITION *in vitro*
Harmaline	75/8h	70–80	$10^{-6}M$
JB 516	25/24h	70–80	$5 \times 10^{-6}M$
Iproniazid	100/8h	50–70	$3 \times 10^{-4}M$
Procaine amide	500/6h	25	$10^{-4}M$
Orthoxine	100/4h	20	$10^{-4}M$
d Amphetamine	10/2h	0	$10^{-3}M$
Ephedrine	100/2h	0	$>10^{-3}M$
Hydralazine	50/6h	0	$>10^{-3}M$

MAO activity measured by serotonin-disappearance technique in rat liver homogenates

possibilities These have not been feasible however either because of the availability of alternate efficient metabolic pathways for the amines or the lack of sensitive and specific methods for measuring the compounds in urine

The results obtained with several drugs which were tested both *in vitro* and in man for MAO inhibitory action are shown in Table 1 listed in order of decreasing potency *in vitro* Harmaline a harmala alkaloid is an example

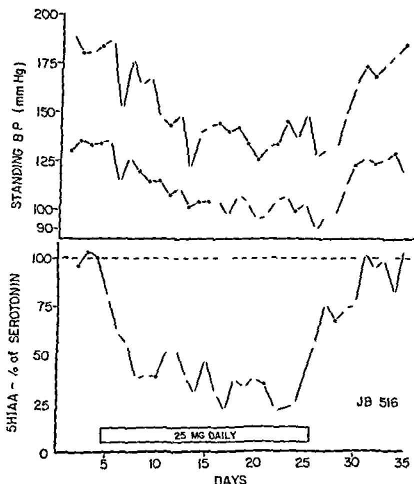


Fig 2 JB 516 in a hypertensive Effects on blood pressure and conversion of serotonin to 5HIAA

of a short acting "reversible" inhibitor while 1 phenyl 2 hydrazinopropane (JB 516 Catron) and iproniazid (Marsilid) are examples of long acting "irreversible" MAO inhibitors Procaine amide and orthoxine are potent inhibitors *in vitro* but exhibit only slight activity in man by the serotonin metabolism test Although amphetamine and ephedrine are frequently referred to as MAO inhibitors they have only weak activity *in vitro* and were totally inactive in man as measured in our procedure Hydralazine a useful antihypertensive drug was found also to be inactive although it contains the hydrazine prosthetic group which is common to many of the

MAO inhibitors now becoming available. Other cardiovascular drugs which were tested and found to be inactive were quinidine, nitroglycerine, peritrate, chlorothiazide, mecamylamine and reserpine.

RELATIONSHIP OF MAO INHIBITION TO CHANGES IN BLOOD PRESSURE

Since production of hypotension seemed to be an effect of many of the MAO inhibitors studied in this laboratory, it was decided to screen some of the more potent of these agents for chemical and physiologic actions in hypertensives.

Discovery of a New Antihypertensive Drug. Early in 1958 a supply of 1-phenyl-2-hydrazinopropane (JB-516) was obtained for study. At that time the compound was undergoing preliminary trial in psychiatric patients as a "psychic energizer." Our plan to administer JB-516 to human hypertensives was viewed with skepticism since the drug had been found to be a pressor agent in the dog. We found in clinical studies that this agent is not only a potent MAO inhibitor in man but also an effective antihypertensive drug. Its effects on MAO and blood pressure in the first patient studied are as shown in Figure 2. There was a striking decrease in blood pressure in the upright position which paralleled the chemical effect. The action on blood pressure closely resembled that obtained with ganglionic blocking agents. In contrast to ganglionic blockade, however, there was a continuous control with a single daily dose orally and an absence of other effects such as constipation, mydriasis, difficult micturition and impotence. The conversion of serotonin to 5HIAA, as well as the blood pressure in the supine and upright position, were measured during short term therapy with the drug in nine hospitalized patients. In each case, enzyme inhibition comparable to that shown in Figure 2 was observed. Generally, there was little change in the supine blood pressure. With one exception, there was a uniform and significant orthostatic lowering of the blood pressure. The drug has now been administered to a larger group of patients for periods up to 8 months; the favorable therapeutic results obtained have already been presented elsewhere.[4] The only significant toxic effect has been the development of temporary red-green color blindness at high dose levels (25 mg./day).

Does MAO Inhibition Produce Lowering of the Blood Pressure? Unfortunately, this question cannot be answered with certainty although hypotension is producible in man with several structurally different MAO inhibitors known to the author. Orthostatic hypotension was a common effect of iproniazid in patients who received daily doses of 150 mg. In a group of eight hospitalized patients treated with 150 to 600 mg./day, however, we were unable to produce as consistent an orthostatic lowering of the blood pressure as noted with JB-516. The inhibition of serotonin conversion to 5HIAA was considerably less than that produced with JB-516 (see Table 1) but patients whose blood pressures responded could not be distinguished from nonresponders on this basis. Recently, our colleagues, Orvis and Tamagna, reported that the combination of chlorothiazide (1.0 gm./day) with iproniazid (75 mg./day) constituted an effective antihypertensive regimen in a small group of clinic patients.

Lately, it was found that certain harmala alkaloids are among the most potent reversible inhibitors of MAO.[5] Since almost all the MAO inhibitors

which have been available are hydrazines it is impossible to separate clearly effects which are due to MAO inhibition from those which depend simply on the hydrazine group A radically different chemical compound such as harmaline offered promise in this respect The drug was administered to five hypertensives for 7 to 14 days in a dosage 75 mg every 8 hours In each case there was an immediate marked inhibition of serotonin metabolism to 5HIAA in the absence of any significant effect on the blood pressure with rapid disappearance of the inhibition after cessation of drug This is in contrast to the slow onset and offset of MAO inhibition seen with iproniazid and JB 516 The results with harmaline at first seemed to prove that a decrease in blood pressure is not a necessary concomitant of MAO inhibition However pharmacologic and drug metabolism studies subsequently revealed that the harmala alkaloids are absorbed incompletely from the gut Thus inhibition could be quite marked in the gut and be inconsequential elsewhere Actually hypotension has been produced in man by the intravenous administration of the harmala alkaloids[9, 10] so that a gross correlation still exists between MAO inhibition and hypotension with this group of compounds

COMMENT

The precise mechanism by which drugs such as JB 516 iproniazid and other MAO inhibitors lower blood pressure is unknown With JB 516 in man the hypotension resembles that produced by sympathectomy Species variation in vascular response may invalidate some of the usual pharmacologic procedures used in dogs to establish site of action of the drug It is probably impossible to explain actions of MAO inhibitors on the basis of changes in the metabolism of only one or even two amines In this connection Dr Leon Goldberg of our laboratory has made the interesting observation that while the cardiovascular activities of norepinephrine and serotonin are not potentiated in the dog with MAO inhibition those of tryptamine and dopamine are markedly potentiated We have now also observed marked potentiation of the pressor actions of the latter compound in man during therapy with JB 516 It is conceivable that dopamine in sympathetic nerves and other tissues may have an important physiologic role in addition to serving as the biologic precursor of norepinephrine As if the situation were not already sufficiently complicated we have recently discovered biogenic amines not previously found in mammals in the urine of patients treated with JB 516 Two of these are tyramine and phenylethylamine The tissue localization of these two amines is unknown although we have learned that tryptamine is present in animal brain liver and kidney In attempting to reconcile the presence of excess pressor amines with hypotension it may be helpful to recall the clinical observation that some patients with pheochromocytoma may have supine *hypertension* but marked postural *hypotension*

Since it is now possible to obtain an accurate index of MAO inhibition in man the enzymatic action of a particular drug or regimen should be established biochemically before MAO inhibition is invoked as producing any of the therapeutic effects which may be observed Also hydrazine compounds are of course notorious in producing alterations in the metabolism of pyridoxine and thereby may inhibit decarboxylation and transamination

reactions of amino acids These alterations are undoubtedly occurring in some of the studies presented here A better understanding of the physiologic consequences of MAO inhibition *per se* will undoubtedly result from further studies with nonhydrazine inhibitors

ACKNOWLEDGMENT

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Evaluation of Hepatic Factors in Hypertension*

B W ZWEIFACH

New York University Bellevue Medical Center

As an outgrowth of a broad program of study on different types of shock the concept was advanced that *vasoactive principles arising in the liver* and kidney represented oppositely acting components of a homeostatic system for the local regulation of blood flow [1] The two principles involved were a vasoexcitor material VEM a product of kidney metabolism identified on the basis of its potentiating effect on the response of the small blood vessels to vasoconstrictor amines and VDM a vasoinhibitory material elaborated in the liver which served to make the vascular smooth muscle cells refractory to constrictor amines Subsequent studies indicated that the vasodepressor activity was related to an iron bearing protein ferritin Ferritin under normal conditions is stored in the liver in a biologically inert disulfide form Under conditions of stress the ferritin undergoes reduction to its free SH form during which process free iron is liberated Mazur and Green[3] are at present of the opinion that the release of iron is the factor responsible for the inhibition of vascular reactivity They have also found[4] that the release of iron from ferritin into the bloodstream is related to xanthine oxidase apparently oxidized ferritin acting as a hydrogen acceptor to interact with reduced xanthine oxidase under special conditions Inasmuch as the release of iron during shock was accompanied by hypoxia of the liver and since normal liver slices subjected to hypoxia under *in vitro conditions also release iron it was assumed that some phase of anaerobic* metabolism was involved

Extensive studies along the same line were carried out on the blood liver and kidneys of animals rendered hypertensive by several experimental methods [5] The studies were conducted on rats and dogs in which the renal artery was partially constricted or in which the kidneys were wrapped in collodion gauze Under these circumstances interference with the circulation to the kidney led within 24 hours to a release of the vasoexcitor principle VEM into the bloodstream VEM continued to be elaborated as long as the tie on the renal artery or the collodion cap was left in place Although the release of VEM usually preceded the rise in blood pressure the bioassay procedure could not be used to quantitate the amount of VEM relative to the severity of hypertension Within 7 to 10 days after renal occlusion blood samples on bioassay showed the presence of increasing amounts of the oppositely acting principle VDM *The identity of this depressor material* was established by fractionating blood samples with specific antiserum to ferritin [6] Thus after the second week of hypertension and throughout the subsequent course of the syndrome the blood contained a mixture of both

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VEM and VDM in which the titer of each of these agents fluctuated Animals which developed malignant hypertension showed elevated titers of ferritin in the bloodstream particularly during the last few weeks of life of the animal

Experimental hypertension induced by the administration of desoxy corticosterone acetate and salt in the rat was not associated with the elaboration of these two vasoactive principles[7] Studies conducted on hypertensive animals in which the adrenals were removed surgically indicated that adrenocorticosteroids were necessary for the formation of the vasoexcitatory principle but evidently not for the elaboration of the hepatic vasodepressor principle

It is obvious that the bioassay findings on these two blood borne agents suggest an etiologic relationship but by themselves cannot establish the validity of this concept. There are a number of features which cannot be readily explained on the basis of the data available Inasmuch as the ferritin component of this homeostatic system is believed to diminish vascular reactivity the only function postulated for such a factor would be to blunt the vasoconstrictor effects of the catechol amines Experiments in which ferritin was injected intravenously into dogs and rats with experimental hypertension failed to show any lowering of blood pressure coincident with the temporary shift in the response of the small blood vessels in the mesenteric circulation.

Direct observational studies of the omentum in the dog and the mesoappendix in the rat indicated that the muscular components of the terminal vascular bed exhibited an initial phase of hyperreactivity during the first few weeks of the syndrome and a subsequent period in which the reactivity gradually returned to normal levels The decline in vascular reactivity was more or less paralleled by a corresponding increase in the blood titer of ferritin It might therefore be anticipated that the administration of ferritin should lower the reactivity of hypertensives to normal levels This however was not found to be true in experiments in which ferritin was given by continuous intra arterial infusion over a period of several hours

The injection of specific antiserum to ferritin might likewise be expected to affect vascular reactivity and possibly blood pressure Thus the inactivation of VDM by specific antibodies should upset the vasotropic balance in the blood and leave the circulation under the influence of the oppositely acting renal principle Experiments using varying amounts of rabbit antiserum were negative in the rat Repeated injections of antisera to ferritin did not appear to influence the syndrome The findings might be criticized on the basis of the fact that it would be extremely difficult to free the blood stream and the tissues of ferritin without encountering the anaphylactic effects of excessive antigen antibody reaction

Another puzzling circumstance derives from the fact that the livers of hypertensives contain unusual amounts of reduced vasoactive ferritin[8] This circumstance was confirmed chemically by direct liver biopsy and by *in vitro* incubation studies of liver slices from hypertensive animals There was no evidence that the livers of hypertensives were subjected to any extended period of hypoxia as occurs during shock In other instances liver under aerobic conditions has been found to release vasodepressor material into the circulation Thus normal liver tissue when subjected to hypoxia from 60 to 90 minutes and then returned to aerobic conditions continues to release vasoactive ferritin into the medium. It is possible that the defect

in hypertension as in the above case is related to an impairment of the inactivation mechanism of ferritin rather than to its formation However no experimental evidence for this possibility has been forthcoming Mazur and Green[9] have suggested that the level of purines in the liver may regulate the amount of iron to be reduced On this basis possibly the elevation of purine levels in the hypertensive might set the stage for utilizing ferritin as an electron acceptor for xanthine oxidase and thereby increase the titer of VDM

Comparable bioassay studies were conducted on blood specimens of man It was significant that patients with essential hypertension malignant hypertension Cushing's syndrome and congestive heart failure all showed the presence of both the renal and hepatic principles in similar proportions to those observed in experimental animals[10] Here again there was no correlation between the severity of the disease as evaluated clinically and the blood titers of these two vasoactive agents

A particularly interesting series of studies were done on three patients with Cushing's syndrome following bilateral adrenalectomy The blood of these patients was studied prior to operation and postoperatively during treatment with desoxycorticosterone acetate and cortisone in amounts designed to maintain their blood pressure at normal levels[11] In these patients the operative procedure was followed by a striking return of the blood pressure to normal levels and an almost complete loss of VDM and VEM from the bloodstream As is well known the blood pressure of such patients could be predictably elevated by increasing the dose of either DCA or cortisone In such instances both VEM and VDM reappeared in the blood stream within 24 hours

Several studies were carried out on patients with essential hypertension who were being treated by several therapeutic regimens including restriction of salt from the diet hypotensive agents and one patient on reserpine In no case was the blood content of VDM and VEM altered by therapy despite the fact that the blood pressure was modestly lowered by such treatment The significance of the blood levels of these principles relative to the blood pressure would appear somewhat questionable in view of the fact that a survey of the blood of patients coming to the outpatient clinic showed a random distribution of VDM and VEM irrespective of the disease entity and the blood pressure[1] There was no correlation between age or sex Blood from healthy controls (medical students nurses) was uniformly negative It is of interest to note that women just prior to during and after the menstrual cycle had high concentrations of VDM in their blood

There is no histologic evidence of liver pathology during essential hypertension Blood levels of transaminase aldolase etc are within normal limits again pointing to the absence of obvious pathology Serum iron levels have not been sufficiently well documented to be of significance in this regard In a recent publication Green and Mazur[9] have cited the fact that the administration of different purines to otherwise normal animals results in a significant increase in plasma iron levels presumably due to the interaction of xanthine oxidase with ferritin No comparable studies have been made on hypertensives this might be a fruitful area for future study

Another recent development may point to a possible role of the ferritin system in the regulation of noradrenalin levels Studies by Axelrod and coworkers[13] have shown that the degradation of adrenalin and noradrenalin

occurs not only by monamine oxidase activity but also by a hitherto undescribed sulfhydryl dependent enzyme O methyl transferase Among the agents which have a catalytic action on this enzyme are certain bivalent cations particularly ferrous iron It is therefore possible that the local release of ferrous iron from ferritin may contribute to the rate of removal or inactivation of catechol amines In this regard it is important to note that ferritin although present in highest concentrations in the liver is present also in almost every tissue of the body Hence with local shifts in blood flow the reduction of ferritin and the concomitant release of iron might represent a mechanism for influencing the local concentrations of vasoactive amines

Although our discussion thus far with respect to ferritin has centered about the iron factor there is some evidence to indicate that sulfhydryl compounds by themselves may exert a regulatory effect on the constrictor activity of adrenalin or noradrenalin [14] Thus mixtures containing low concentrations of cysteine or glutathione and adrenalin or noradrenalin do not exhibit the usual vasoconstrictor effects of these amines when applied locally The evidence suggests that these sulfhydryl agents may serve as anti oxidants and that oxidation of the catechol amines is required for their musculotropic effects Another possibility is that a change in local redox potential and the availability of free SH groups may activate or inactivate systems concerned with the oxidation of other vasoactive sulfhydryl compounds such as ferritin

It is apparent that we have no explanation for the appearance of ferritin in the bloodstream of hypertensive animals and hypertensive patients The precise relationship of ferritin and iron mechanisms to the factors responsible for the elevation of blood pressure and altered vascular reactivity likewise are open to question However the fact that these agents appear regularly and predictably in most forms of experimental hypertension as well as in human hypertension makes it imperative that further attempts be made to establish the importance of these agents *per se* or the particular metabolic sequence responsible for their elaboration

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The Relationship of Trace Metals to Hypertension

MARVIN J SEVEN

Hahnemann Medical College and Hospital

The broad realm of metal binding agents has now extended into almost every field of clinical medicine[1] Of the many known applications we are reminded continually of one interesting possibility that these agents have antihypertensive properties This suggestion stems to a great degree from studies with disodium ethylene diamine tetra acetate (disodium EDTA) and its derivatives and from studies with certain sulfhydryl containing com pounds We shall explore this today There is further evidence for the action of certain metals on the vascular system Perhaps the two factors metals and hypertension are related It may be on the other hand that this approach is unrealistic

METAL-BINDING AGENTS

Almost all known antihypertensive agents except the ganglionic block ing agents show structural potentialities to bind metals, either through nitrogen atoms and/or hydroxyl groups or through sulfhydryl groups[3] Many of these will do so *in vitro* each agent with an affinity for a certain spectrum of metals This spectrum depends upon several factors the most important being the relative position in the molecule of the chelating or complexing groups and upon steric factors relative to each metal[4] Not all of these com pounds are known to bind metals *in vivo* Some are rapidly metabolized others have active metal binding groups tied up through another form of linkage still others exhibit metal binding properties weaker than the competitive action of certain body proteins

Of all organic compounds known to bind metals *in vivo* not all are

antihypertensive agents Some exhibit this property only under certain conditions For example certain agents will lower blood pressure only in selected laboratory animals others appear to do so only in anesthetized hypertensive animals [5, 6] The mere act then of metal binding *in vivo* is not sufficient evidence for antihypertensive action This suggests that a specific metal or group of metals may be involved If this is true the relative activity in lowering blood pressure might depend on the metal spectrum of each specific agent For some agents hydralazine as an example the spectrum is narrow For others the spectrum appears to be broad but actually is narrow in terms of firm *in vivo* bonds These agents might act in lowering blood pressure then through binding of one or a few specific metals Other agents whose *in vivo* spectra do not include this metal or group might be inactive

MECHANISMS OF BINDING ACTION

To carry our speculation further antihypertensive action does not have to follow the actual binding of a metal Several things can happen

1 Binding may take place at a cellular level removing a vital metal from its function in an enzymatic process More and more we are becoming aware of the action of certain metals as metalloenzymes or as necessary catalysts to enzyme systems [7]

2 A metal may be bound at some place in the body and carried via the body fluids in this form to a cell where it is broken off from the binding agent (ligand) and released to inhibit an enzymatic process This severance of bonds would be the result of a greater competitive affinity of certain body proteins for the metal Certainly some metals are thought to act in such an inhibitory manner on cellular enzyme systems as for example mercury in renal tubular cells [8]

3 A metal bound in the body to an antihypertensive agent or to a body protein could act as a unit to inhibit an enzyme system by presenting the proper molecular configuration to a protein complex Certainly this is not a new concept in enzymatic inhibition For example in the field of antibacterial agents the ferric chelate of 8 hydroxyquinoline appears to be the inhibitory agent in the bacterial cell [9] Also observed potentiation of the action of epinephrine on the isolated rabbit intestine by a variety of compounds has seemed directly related to the presence of copper chelates [10]

4 Finally the mobilization of metals in body fluids by metal binding agents might result in circulation of metals in the inorganic form or loosely bound to plasma proteins This would be the result of an anticipated interchange between plasma or tissue ions and bound ions as those weakly bound are exchanged for those held by firmer bonds Certainly there are known vascular responses to inorganic and loosely bound metals (*vide infra*)

It can be expected then that antihypertensive action might result from mechanisms other than the *removal* of a metal ion

METAL-SPECTRA OF AGENTS

To examine the known effects of specific metals on the cardiovascular system we may eliminate some from our consideration at this time by examining the metal spectra of binding agents with known antihyperten

sive action With regard of disodium EDTA and its specific chelates depressor action has been reported in anesthetized hypertensive rats[3] and in normotensive and hypertensive humans[11 1 13] However the evidence here is controversial since some investigators have reported a pressor action[14] In our prolonged studies with disodium EDTA its chelates and derivatives we have never observed significant blood pressure changes in *normotensive individuals It has been suggested that only some of the less* tightly bound metals (as chelates of disodium EDTA) show depressor action[3] This may be related in part to the fact that we are accumulating evidence to indicate that even the strongest of the chelates of disodium EDTA are not stable *in vivo*[15 16 17] Although this may have been anticipated in one study the control group which received inorganic metals cannot be considered to be comparable[3] For these reasons I should like to eliminate this series of compounds from our consideration

Another compound of interest is 2 3 dimercapto propanol (BAL) which *forms a chelate ring between a metal and its sulfhydryl* groups[18] *The* evidence for vascular action is highly controversial some investigators reporting pressor activity and others depressor action[6 19 0 21] We may comment in passing that divergent reports such as these usually are resolved by careful painstaking studies

Perhaps a look at hydralazine will narrow the field of metals for us since an outstanding action of this compound is the binding of iron copper tin vanadium silver nickel manganese and mercury[2] There is further suggestive evidence for its metal binding activity *in vivo* since some of its toxic *reactions are identical to those of disodium EDTA*[3 4 5] *Some* change in urinary metal output during therapy has been reported but evaluation of this report must await more information on the methods employed[6] Others of the commonly employed antihypertensive agents with metal binding properties have not received as much evaluation

ACTION OF SPECIFIC METALS

It can be seen that we have not narrowed the metal spectrum for consideration to any degree by a careful look at certain of the metal binding agents Turning now to metals in the inorganic form there are some which show action on vessels Magnesium is known to be a potent vasodilator[7 8] In the therapy of hypertension magnesium sulfate is commonly employed for this purpose *It may be that the magnesium chelate of disodium EDTA* or of its ethanol derivative *(HEDTA)* will provide a better vehicle for administration of this ion[9] Cobalt is known to have a vasodilatory action[0] Vanadium in the form of sodium vanadate may act as a peripheral vasoconstrictor[31] A recent study of interest has shown the action of copper sulfate to constrict coronary vessels in the isolated rabbit heart an effect which can be abolished by hydralazine and other copper binding agents[3] It is suggested that the resultant coronary dilatation in this study might be caused by binding of the metal in the vessel wall Of several ions tested only Cu^{++} showed constrictor activity

A still more direct approach *would be the* examination of body tissues or fluids for specific trace metal content in normotensive and hypertensive subjects One study has shown serum magnesium levels to be somewhat lower than normal in essential vascular hypertension[33] Some evaluation of

urinary output of metal ions has been done but again the methodology is unclear[34, 3] Such a study done with the necessary careful attention to details of reagents precision accuracy and recovery of added metals would be a time consuming venture but one of great importance to this field

It can be seen now that we have not narrowed the scope to one or two metals Obviously much more work has to be done For our purposes today we may say that some of the more common trace metals seem to play some role in pressor and depressor action Only one of the more rare metals vanadium shows similar activity on vasculature Although a more rare metal eventually may hold the key to the problem of etiology and therapy in hyper tension this does not seem likely at this time

RELATED STUDIES

It is possible that an answer to this problem may be reached by some ancillary study Antihypertensive effects are associated in some ways with diuretic action For example the chlorothiazide molecule shows potentiali ties for metal binding Some recent studies with thioctic acid (lipoic acid) a potent metal binding agent through sulfhydryl groups have suggested a diuretic action for this compound However the results are inconstant and the evidence remains controversial[36, 37] Occasionally investigators working with disodium EDTA and calcium disodium EDTA have suggested to us that these compounds have diuretic action In our studies we have not found this to be true Many reports have accumulated on the relationship of metals to atherosclerosis and the influence of metal binding agents on hypercholesterolemia.[3] In another sphere substances which potentiate the effects of epinephrine have been found to be chelating or complexing agents and this potentiation seems strongly related to this effect[1] The influence of metals on monamine oxidase and other related enzymes is of great impor tance to this field and is discussed in another presentation in this Symposium

SUMMARY

That most of the antihypertensive agents have metal binding properties does not seem coincidental especially in view of the known activity of metals as metalloenzymes and as catalysts in other enzymatic processes This consideration has followed a similar pattern in the field of antibacterial agents in recent years and it is now recognized that approximately 75 per cent of antibacterial agents have metal binding properties in most cases thought to be the significant mode of action[38] The fact that we have not been able to center our attention on one or a very few metals as significant in the etiology and/or therapy of hypertension does not rule out our thoughts on the possible vasopressor or depressor action of several of them Rather it will seem wise to press for a careful systematic study of all potential agents to bind the more common metals recognizing that this binding action could result in metal activity *in vivo* in several different ways

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A Summary of the Laboratory Observations on Humoral Agents as a cause of Hypertension

GEORGE E WAKERLIN

American Heart Association

Several humoral agents which may be pathogenetic in hypertensions have been discussed this morning and there will be discussion of other humoral agents this afternoon First there is the blood pressure regulatory or antihypertensive function of the kidney This may possibly operate through a hormone or humoral agent although this seems unlikely at pres ent This was the function of the kidney to which Dr Grollman briefly referred this morning Then there is the hypothalamic anterior pituitary response to stress which will be discussed this afternoon As you know this mechanism operates through the release of certain hormones Then there are adrenocortical hormones which were referred to this morning and will be considered again this afternoon Another humoral agent is norepineph rine and there are other amines such as pherentasin referred to by Dr Schroeder as increased in patients with essential hypertension and more so in patients with malignant hypertension Monoamine oxidase has been

thoroughly discussed this morning as have hepatic factors Sodium and other electrolytes appear to have a relation to the pathogenesis of hypertension which was referred to this morning and will be discussed again this afternoon And finally the possibility that certain trace elements may have a pathogenetic role in hypertensions was discussed by the immediately preceding speaker Accordingly my summary will not concern itself with these humoral agents

EXPERIMENTAL RENAL HYPERTENSION

With reference to the pathogenesis of experimental renal hypertension Figure 1 shows that constriction of the remaining renal artery of a unilaterally nephrectomized dog produces hypertension as Dr Goldblatt showed many years ago On removal of the constriction the blood pressure comes down to normal as has also been shown for the rabbit If the renal

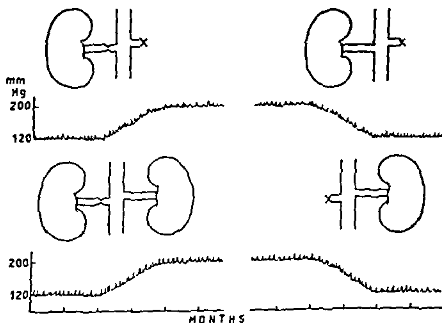


Fig 1

artery is constricted on one side as indicated in Figure 1 in an occasional dog the blood pressure will remain elevated permanently If the constricted kidney is removed the blood pressure will come down at least in some of the dogs This also is true in other species but less commonly so because the opposite kidney tends to develop changes These experiments suggest that the kidney with a constricted renal artery produces some kind of pressor substance or humoral agent which is pathogenetic in this hypertension and that it is not decreased renal function which is important

Renin and Angiotensin

The most likely substance of course is renin and for the benefit of some of the clinicians in the audience may I point out as indicated in Table 1

TABLE 1

Alpha Globulin

Renin ⟶ ↓

Angiotensin I ⟶ II

(Asp Arg Val Tyr
Ileu His Pro Phe)

that renin acts as a proteolytic enzyme on an alpha globulin to split off a polypeptide known as angiotensin I which is composed of ten amino acids Then an angiotensin activator splits off two more amino acids to give angiotensin II which is directly vasoconstrictor

In 1950 Blacket Pickering *et al*[1] showed that if hog renin solution is infused intravenously into the unanesthetized rabbit a persistent increase in blood pressure for sixteen to eighteen days is produced (Fig 2) But the amount of renin infused was such that with methods of assay of renin available then and now a detectable difference in plasma renin concentration between the rabbit before and during the infusion could not be shown This

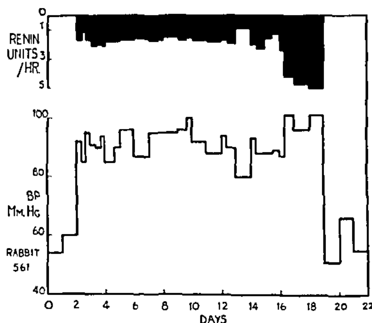


Fig 2

TABLE 2

ANGIOTENSIN (U/L)	NORMO TENSIVE DOGS	EXP REN HYPER DOGS
0 00	3	0
0 03-0 08	4	0
0 10 0 40	0	5
0 50 0 80	0	4

Data from Skeggs Kahn and Shumway

illustrates one of the difficulties involved in ruling renin in or out as a patho genetic agent in chronic experimental renal hypertension

More recently Skeggs and coworkers[2] assayed the angiotensin content of a dialysate of blood from normotensive dogs and renal hypertensive dogs and showed a significant difference between the two as indicated by Table 2 Unfortunately the longest hypertension in this series was only 90 days and most of the hypertensions were less than 50 days which is within the period of acute hypertension This experiment should be repeated with dogs that are chronically hypertensive since plasma renin is known to be in creased in acute experimental renal hypertension Kahn Skeggs and co workers[3] also studied the angiotensin content of the dialysate in normo tensive humans and in humans with severe essential hypertension and found some increase in angiotensin (Table 3) The p value was a modest 0 03 These results suggest that renin and angiotensin may play a pathogenetic role not only in experimental renal hypertension but in essential hyper tension

Antirenin in Experimental Renal Hypertension in Dogs

Our research group almost twenty years ago approached this problem in a somewhat different way[4] We reasoned that since renin is a protein heterologous renin parenterally administered ought to give rise to an anti body (antienzyme) or antirenin used in a different sense from that in which Dr Schroeder used the term this morning Figure 3 shows our first experi ment At the left the intravenous injection of what would now be 2 dog units of hog renin mixed with 1 cc of normal dog plasma into an anesthe tized assay dog produced a typical increase in blood pressure The second injection involved the same amount of renin which was mixed with 1 cc of plasma from a dog repeatedly injected intramuscularly with hog renin for

TABLE 3

ANGIOTENSIN (U/L)	NORMO TENSIVES	HYPER TENSIVES
0 00	10	4
0 01	1	0
0 02	9	5
0 03	2	3
0 04	0	2
0 05	2	2
0 06	0	2
	p = 0 03	

Data from Kahn Skeggs Shumway and Wissembaugh[3]

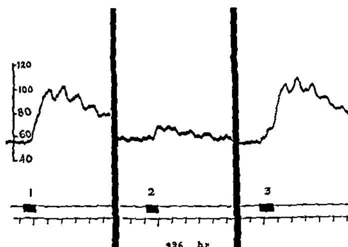


Fig 3

several months There was only a slight increase in blood pressure The third injection was a control similar to the first injection This experiment illustrates that it is possible to produce an antirenin to hog renin in the dog Goldblatt in Cleveland and Helmer and coworkers in Indianapolis later obtained similar results Table 4 shows the pressor neutralizing effects of various antirenins on different renins Thus antirenin to hog renin not only neutralizes hog renin but also dog renin This is important since if hog renin is injected into a renal hypertensive dog and if an altered secretion of renin plays a pathogenetic role then a reduction in blood pressure should result from neutralization of endogenously produced dog renin by antirenin On the other hand monkey renin and human renin are not neutralized by the antirenin to hog renin Conversely antirenin to human renin produced in three species neutralizes only human renin and monkey renin and no subprimate renins These relationships will be referred to again below

Figure 4 shows the result of an early experiment on the treatment of

TABLE 4 NEUTRALIZATION OF THE PRESSOR EFFECT OF RENIN WITH ANTIRENIN

Antirenin against	Renin from							
	Rat	Rabbit	Hog	Goat	Cat	Dog	Monkey	Human
Hog Renin in Dog	+	+			+	+	0	0
Hog Renin in Monkey						+	0	0
Hog Renin in Human	+	+			+	+		0
Hog Renin in Goat			+	0		+		0
Human Renin in Rabbit	0	0	0		0	0		+
Human Renin in Dog	0	0	0		0	0		
Human Renin in Monkey			0			0	+	

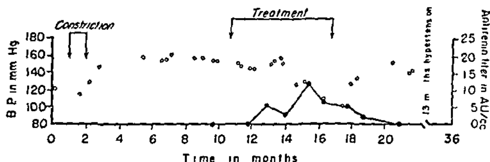


Fig. 4 Treatment with semipurified hog renin from cortex

a renal hypertensive dog with injections of hog renin. As the antirenin titer increased to a maximum the blood pressure decreased to a normotensive level. After treatment was stopped the blood pressure gradually went up as the antirenin titer decreased. We have similar experiments in 125 dogs accumulated over a period of 18 years with renins of different species and degrees of purity. This is not a nonspecific foreign protein effect. Antihypertensive results were not obtained with control extracts prepared from other tissues or with heat inactivated renin solutions. There were no toxic effects from the renin or control injections. Indeed the semipurified hog renins which we used had a purity similar to that of the first preparations of insulin used on patients.

We tried the reverse experiment to see whether antirenin to hog renin in the dog would prevent the development of experimental renal hypertension following standardized constriction of the renal arteries. Figure 5 shows a successful prophylaxis. After treatment was stopped and the antirenin titer decreased to zero the blood pressure gradually increased to a distinctly hypertensive level. We have performed 100 such experiments in dogs.

Goldblatt and Helmer have obtained similar treatment results and Goldblatt similar prophylaxis results in experimental renal hypertension.

Figure 6 shows the effect of high titer homologous antiserum containing antirenin to hog renin injected subcutaneously into a dog with experimental renal hypertension of nine years duration. The blood pressure of the dog

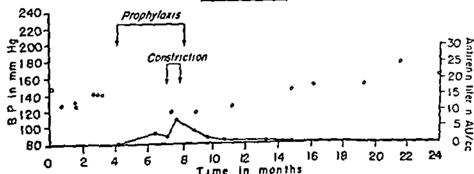


Fig. 5 Prophylaxis with crude hog renin from cortex

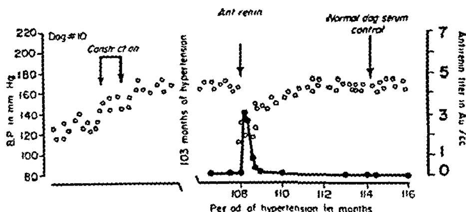


Fig 6 Passive transfer of antirenin

was reduced to the normotensive level simultaneously with the appearance of the passively produced antirenin titer A control injection of dog serum produced no fall in blood pressure We have conducted 54 similar experiments on chronic renal hypertensive dogs In the aggregate these findings with antirenin suggest that in experimental renal hypertension even of long duration renin plays a pathogenetic role

Antirenin in Experimental Renal Hypertension in Monkeys

Since antirenin to hog renin does not neutralize monkey renin hog renin therapy should be ineffective in experimental renal hypertension in the monkey Figure 7 shows such a negative result although an antirenin titer of 18 antirenin units per cc of serum against hog renin was obtained Five other renal hypertensive monkeys showed a similar negative result Figure 8 shows a negative prophylaxis experiment with hog renin in the monkey Five other monkeys showed a similar negative finding Since human and monkey renins are similar antigenically these experiments suggest that the negative results reported for hog renin therapy in humans with essential

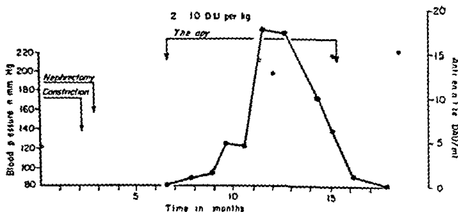


Fig 7 Treatment in monkey with semipurified hog renin from cortex

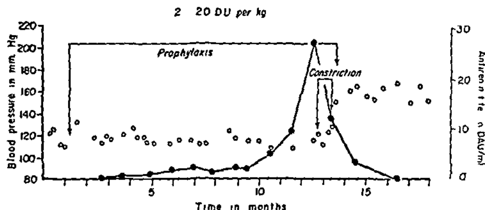


Fig 8 Prophylaxis in monkey with semipurified hog renin from cortex

hypertension in no way rule out the possibility that renin may play a pathogenetic role in essential hypertension

Next our group tried the experiment of injecting human renin into monkeys As I mentioned earlier human and monkey renins are very similar antigenically but there was a possibility that they might be sufficiently different so that an antirenin to human renin might be produced in the monkey This proved to be so[5] Table 5 indicates that with the appearance of antirenin an antihypertensive effect was obtained in four monkeys treated with human renin (+± means reduction in blood pressure half way to normotension + one third of the way)

Table 6 shows that passive immunization with antirenin to human renin produced antihypertensive effects in seven monkeys whereas control injections were without antihypertensive effect in six hypertensive monkeys (+++ means reduction in blood pressure to normotension) *These results indicate that renin plays a pathogenetic role in experimental renal hypertension in the monkey*

ANTIRENIN IN SPONTANEOUS AND PYELONEPHRITIC HYPERTENSIONS IN DOGS

Over a period of twenty years we were able to collect five dogs with what we consider to be spontaneous or essential hypertension" As far as we could tell these dogs resemble patients with early essential hypertension Figure 9 shows the results of our first experiment with hog renin therapy in a spontaneously hypertensive dog With the production of antirenin to hog renin the blood pressure decreased to a normotensive level and as the

TABLE 5

MAXIMUM ANTIRENIN TITER (AU/cc)	ANTIHYPERTENSIVE EFFECT OF CRUDE HUMAN RENIN IN MONKEYS
0 8	+±
3 3	+±
7 0	+
12 0	+

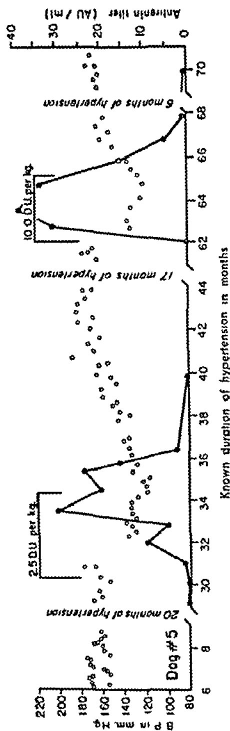


Fig 9 Treatment with semipurified hog renin

TABLE [illegible]

Maximum antirenin titer AU/cc: Vs human	Vs hog	Antihypertensive effect of heterologous antirenin [illegible]
0	0	0
0	0	0
0	4	0
0	–	0
0	15	0
0	19	0
0.[illegible]		–±
0.5		0 –
0.[illegible]	6.[illegible]	—
0.[illegible]	0.5	—
0.4	1[illegible]	—
1.4		–±
[illegible]2		—

antirenin titer decreased, the blood pressure increased. A second course of hog renin produced a similar result. The same findings were obtained in four other spontaneously hypertensive dogs.[8]

Reductions in blood pressure were also obtained by passive immunization of the spontaneously hypertensive dogs with high titer antiserum containing antirenin to hog renin. No reductions occurred with a similar quantity of antiserum of low titer producing a very low titer of antirenin passively (Fig. 10).

We likewise obtained similar results with active therapy and passive immunization in five dogs with hypertension associated with chronic bilateral pyelonephritis, suggesting that this hypertension, as well as spontaneous hypertension in the dog, is on a renin basis.

OTHER HUMORAL AGENTS

With reference to other humoral agents, renotrophin should be mentioned. Renotrophin is a substance hypothesized by Braun-Menéndez to be a by-product of protein metabolism. He believes that renotrophin pro-

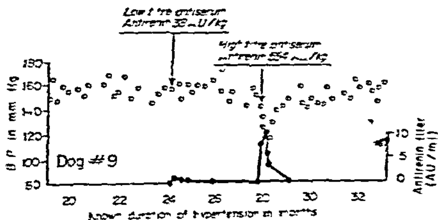


Fig. 10. Passive transfer of antirenin.

duction is stimulated by the male sex hormones thyroid secretion certain anterior pituitary hormones and high protein diet According to Braun Menendez when renotrophin concentration of the plasma is increased and renal tissue is decreased or prevented from hypertrophying hypertension results Braun Menendez hypothesis does not suggest how the hypertension is produced but he believes that renotrophin plays a pathogenetic role not only in experimental renal hypertension but in other hypertensions

More recently Hajdu and coworkers[8] using the isolated frog heart as a test organ found in the plasma of patients with essential hypertension a cardiotonic substance which is present in the globulin fraction of the plasma proteins Whether this substance plays a role in the pathogenesis of essential hypertension remains to be determined

CONCLUSION

More work in the laboratory and clinic is needed to determine which humoral agents are pathogenetic in human hypertensions particularly essential hypertension since the only humoral agents that we now know to be pathogenetic in human hypertension are norepinephrine in the unusual hypertension of pheochromocytoma and aldosterone in the very rare hyper tension of primary aldosteronism

ACKNOWLEDGMENTS

The research herein reported on renin intirenin as coming from the University of Illinois has occupied almost 20 years and has been performed by more than 100 colleagues and graduate students the principal contributors being Drs R O Burns M H Frank E W Hawthorne C A Johnson W G Moss E A Ohler and R W Sevy and Mr L Graham

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TABLE 6

MAXIMUM ANTIRENIN TITER (AU/cc)		ANTIHYPERTENSIVE EFFECT OF HETEROLOGOUS ANTIRENIN TO CRUDE HUMAN RENIN IN MONKEYS
TO HUMAN	TO HOG	
0	0	0
0	0	0
0	4	0
0	7	0
0	13	0
0	19	0
0 2		+±
0 3		0 +
0 7	6 3	++
0 7	0 8	+++
0 9	1 0	+++
1 4		+±
3 2		+++

antirenin titer decreased the blood pressure increased A second course of hog renin produced a similar result The same findings were obtained in four other spontaneously hypertensive dogs[6]

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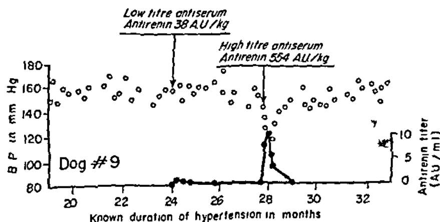


Fig 10 Passive transfer of antirenin

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Discussion

Arthur Grollman *Moderator*

A C Corcoran	Milton Mendlowitz
J Richard Crout	George R Meneely
Harriet Dustan	Henry Schroeder
Robert Gaunt	Marvin Seven
Harry Goldblatt	Albert Sjoerdsma
Phyllis Hartroft	George Wakerlin
G M C Masson	Benjamin Zweifach

Dr Grollman In this morning s session which deals with the basic concepts of the etiology of hypertension you have all no doubt noted the inconsistency of many of the points raised For example monamine oxidase has been mentioned as a potent agent which inhibits hypertension while others consider it as possibly a causative agent in hypertension We might start by asking Dr Schroeder how he would explain this paradox

Dr Schroeder I m going to make a suggestion Monamine oxidase inhibitors may or may not act through monamine oxidase inhibition A good many of the ones that Perry has worked on in our laboratory contain decarboxylase inhibitors as well And a good many of them also inhibit histidine decarboxylase and almost all of them inhibit histaminase or diamine oxidase

Also there is a tendency these days to talk about monamine oxidase inhibitors as alleviating schizophrenia or depression And yet we don t know that it s because they are inhibiting monamine oxidase at all That s why I can t see that there s any paradox here until we have determined exactly what these things do

Dr Sjoerdsma I think we re in total agreement that it s crucial to relate specifically to monamine oxidase inhibition and I hope I indicated in my presentation that this was what we were attempting to do I would certainly agree that these compounds have other actions We studied hydrazines for decarboxylase activity and thus far the only one we studied that has marked activity *in vivo* is hydralazine JB 516 doesn t have any significant decarboxylase inhibitory activity in the intact animal as far as we can tell in preliminary experiments I think that we are still dealing with one or two enzymes here The same criticism can be made for the specificity of any drug For example when one talks of metal binding one can raise the question of another hundred types of action nevertheless this shouldn t stop our progress along specific lines

Dr. Grollman Would Dr Sjoerdsma agree that so far as the peripheral vasculature is concerned the effect of monamine oxidase inhibitor would be to increase the blood pressure and not decrease it? It ought to keep more epinephrine available by causing more constriction and without any compensatory mechanisms ought to increase the blood pressure not decrease it

DR SJOERDSMA I agree that this is what it ought to do The fact that it doesn t do that makes it even more interesting It may be that all the peripheral actions on blood pressure of monamine oxidase inhibitors have to be explained in terms of alterations in what happens to norepinephrine We know that other amines are involved in the function of the nerves most likely the precursor of norepinephrine which has always been assumed to have its function in being a relatively weak agent in its own right Nonetheless when one administers a monamine oxidase inhibitor to a human and then injects various amines one finds no potentiation of norepinephrine pressor responses And as Horwitz in our group did recently it induces a fantastic potentiation of the pressor response to dopamine to such an extent that it places dopamine in a monamine oxidase inhibited individual in the same category as norepinephrine in terms of physiologic potency Getting back to your original point however I think one should try to explain the action of these drugs in terms of norepinephrine alone although we know that numerous other amines are involved Indeed in patients who are inhibited in this manner we have found several decarboxylated amino acids to be present in their urines that have never been found in mammalian organisms previously What their role in blood pressure is I don t know but it may be considerably more complicated than norepinephrine alone With norepinephrine itself you can set up theories which would fit lowering of blood pressure by something which affects its metabolism I personally favor monamine oxidase as being more important than O methyl transferase although this is just a hunch If it is you have the situation where the excess of an amine can block its own action That would be a possibility where the transmission can be blocked because there s too much of the transmitter We know that administering these agents causes rises in norepinephrine content of nerve and tissue This is because the material is not being metabolized On the other hand the fact that it accumulates in the tissue may indicate also an effect on binding mechanisms so that these agents may alter binding in tissue and actually affect transmission Finally it s perfectly possible of course that they merely compete with norepinephrine in addition to altering its metabolism and we have wondered whether monamine oxidase might actually be the receptor or something of that sort

DR. SCHROEDER Some years ago we rather naively got the idea that you could lower the blood pressure by flooding the system with an amine of lesser vascular potency than whatever was constricting blood vessels be it angiotonin pherentasin or norepinephrine We gave infusions of isoamylamine which is a rather weak vasoactive substance It has a potency of 1 compared with 1640 for norepinephrine Interestingly enough in hypertensive dogs and hypertensive man it was a depressor substance but in normotensive dogs and normotensive man it was a pressor substance slightly pressor in large amounts We thought at that time that we had flooded the end organs with an amine of low potency I know of 14 amines that are apt to perform conceivably as monamine oxidases all of which are presumably naturally occurring and a great many more synthetic ones I don t think we can answer this question at the present time

DR SJOERDSMA And we don t know where they re localized in the body

DR GROLLMAN In view of the publicity which has attended the introduc

tion of compound JB 516 Dr Sjoerdsma I m sure many of our listeners would like to know if you think this is a practical drug in the treatment of hypertension Will its toxic effects in the large doses which you use compared to the much smaller doses used in psychiatric practice preclude its use as an antihypertensive agent?

DR SJOERDSMA I haven t been in this field as long as you have Dr Grollman but I ve been in it long enough to know that anyone who has the audacity to think that short term therapy with any particular drug is going to give enough evidence as to how useful this drug will be in the long term or how completely practical it is is fooling himself I can only say that in our hands in about 25 patients treated for 8 or 9 months under careful observation we have been most impressed with the potency of the agent in producing orthostatic lowering of the blood pressure There have been a few exceptions to that There have been surprisingly few other effects particularly a lack of the usual effects one associates with ganglionic blockade that is loss of sexual potency constipation changes in the pupils and so forth

DR GROLLMAN I know Dr Mendlowitz is anxious to talk about his brain child O methyl transferase which has recently been heralded as the cause of hypertension

DR MENDLOWITZ This is not my brainchild We merely suggested this because we were aware of the possible importance of the enzymes in the process of increased vascular reactivity which Dr Crout spoke about this morning We knew that Marsilid or iproniazid was a potent monamine oxidase inhibitor and we tried to see whether we could increase sensitivity to norepinephrine in normotensive subjects by administering large amounts of iproniazid We gave as much iproniazid as we could to the human subject intravenously without producing toxicity In fact we did produce toxicity in some We were unable to see any change in the peripheral sensitivity to norepinephrine Of course this does not mean that the reactions in the nervous system might not be different. But since we consider the peripheral vascular reactivity to norepinephrine as having a central role in the etiology of essential hypertension we feel fairly convinced that monamine oxidase is not involved in the process If monamine oxidase is not involved in the process the only enzyme on the horizon is O methyl transferase It may not be this enzyme at all but something that we haven t even conceived of as yet

DR GROLLMAN Dr Corcoran you weren t here this morning so I d like to give you a chance to speak on your concept of the etiology of essential hypertension

DR CORCORAN Dr Wakerlin drew our attention again to the renal pressor system and as you know we ve been interested in that for a long time It reminds me of the trouble the Lord had with the Jews Periodically a prophet would come along and remind them that they shouldn t go off after these strange gods i e these trace metals these unusual enzymes but come back to a central issue like angiotonin and let s clear that business up And I think that was part of the point of Dr Wakerlin s statement There is one question I would like to ask him As some of you may know there has been

a slight difference of opinion between Dr Wakerlin and our group on the occurrence of spontaneous essential hypertension in dogs since those dogs we found with spontaneous hypertension had pyelonephritic renal hypertension Doesn't the fact that treatment was so effective in the spontaneous renal hypertensive dogs you had probably suggest this?

DR WAKERLIN We had ten dogs which we collected over a period of 20 years from more than 2000 dogs that we examined Up to the time that we autopsied these animals we thought they were all spontaneously hypertensive because their renal functions were normal We saw nothing to indicate that there was any renal abnormality We waited until we sacrificed the animals and then we made a diagnosis of essential hypertension in five dogs because we saw no evidence whatever of pyelonephritis in these five but we did find pyelonephritis in the other five We also found no cause of hypertension that the pathologist can determine in any other area of the body This was the basis then for our saying that these five dogs were spontaneously "essentially hypertensive" Nevertheless they did respond to the injections of renin I think there is only one way to settle this question so far as our present information is concerned and that is to do what Hoobler is now trying to do—to collect sufficient amounts of human antirenin to do the same experiment in a small group of patients with essential hypertension by passive transfer that we have done in a small group of monkeys The other possibility of injecting monkey renin into humans and getting an antirenin to monkey renin which ought to neutralize human renin is just about out of the question because we calculated that to get one satisfactory experiment in one human would take the kidneys from 250 000 monkeys since the concentration of renin in the monkey kidney is still less than it is in human kidney Now of course one other approach that I think is much more of a possibility is for one of the biochemists to find a good inhibitor of angiotensin and if he finds it and if it has an antihypertensive effect this would be the answer However I would like to point out that it is still possible that renin may operate through some mechanism other than the angiotensin mechanism to produce hypertension

DR CORCORAN Dr Wakerlin you are suggesting that the next line of endeavor should be something that blocks angiotensin formation by conversion of angiotensin 1 to angiotensin 2 in answer to Dr Grollman's question

DR WAKERLIN About 15 years ago we tried to produce some anti angiotensin and we did not succeed at that time We assumed that the angiotensin molecule was probably too small to be antigenic but a little later on we were able to produce an antivasopressin Now we learn that these two molecules are the same size each has three amino acids or thereabouts in it I wonder whether Dr Goldblatt might not try again to produce some anti angiotensin without hooking it to a larger molecule I would think that maybe we didn't use a large enough quantity

DR SCHROEDER Swinging the question around a little bit if you want an anti angiotensin I would suggest that you use a trace metal binding agent which has the strongest stability constant on copper The reason I suggest this is that several binding agents will inactivate angiotensin slowly *in vitro*

so that the angiotensin is no longer active on the isolated smooth muscle of the rabbits aorta This is not an effect on the rabbits aorta itself because it takes several hours for the reaction to be complete Such things as EDTA are rather weak anti angiotensins such things as nitroprusside which Dr Corcoran has used clinically are strong ones so are such things as some of the sulfhydryl binding agents and the hydrazines particularly hydralazine

DR GROLLMAN Turning to other matters discussed this morning Dr Seven what about the excessive metal content of the kidney which is supposed to have been found in adults over the world? Do you think it has any relationship to the etiology of hypertension?

DR SEVEN I dont know Dr Grollman We are in a field here that is of particular interest to myself and Dr Schroeder and maybe we are on a side track as Dr Corcoran implied There has been some thought about the possibility of the accumulation of metals in different parts of the body particularly the kidney as having etiological significance but I know that this has been related by another member of the panel to the aging process I know that there is a specific damage pattern produced by cadmium in the kidney but I think that the damage pattern is not of vascular but of tubular action I cannot comment on this any further

DR GROLLMAN Does anyone else on the panel care to comment?

DR WAKERLIN There have been some results published recently by Griffith and his group at the University of Southern California They have found several significant differences in the amounts of trace elements in the myocardium and in the aortae of patients with essential hypertension as contrasted with normotensives of the same age groups which would presumably rule out the aging factor Whether these play any role pathogenetically no one knows

DR SCHROEDER Dr Grollman based on a series of 400 autopsies collected by Tipton and her group at Oakridge National Laboratories 140 bodies from the area that I collected and 70 from Africa that Dr Perry collected I think that we can say that cadmium does increase with age in the kidney This is found all over the world in city dwellers at least with the exception of some adults in one section of Africa There is none in babies and if you are looking for an enzyme inhibitor that is present in the whole population of the urban dwellers of the world youve got it right there It is a strong dopa decarboxylase inhibitor as well as an inhibitor of other enzymes

DR SEVEN Dr Schroeder and Dr Perry reported that some cations were present in excess in the urine of hypertensive patients One of these was cadmium but there was also manganese and I think magnesium and a few other bivalent cations Such cations as manganese cadmium and cobalt all bivalent are necessary in the O methylation of norepinephrine

DR CROUT Id like to make a few comments relative to some general biochemical principles which I think may bear on the discussion this morning One is that if you are going to implicate enzymatic function in any

abnormality you must demonstrate that among other things the substrate is normally present that it is metabolized by the enzyme that the metabolite is inactivated by the enzyme and that therefore enzymatic inhibition fails to inactivate the substrate By this I mean that if other pathways are available for the metabolism of this substrate enzymatic inhibition of one pathway may have little to do with how the thing is handled over all I would also like to say that every enzyme system which utilizes ATP requires a divalent ion either magnesium or manganese or something like this for its action A catechol methyl transferase requires the action of ATP and an active methyl donor for its action and quite naturally would then also require a divalent ion There is another point which I think pertinent in this discussion on biochemistry We should recognize that practically all of the comments this morning are speculation This is the biochemical age and a failure to find an explanation in anatomic or physiologic abnormalities will naturally lead one to turn to a biochemical one Surely if the pathologists can t see it maybe the biochemists can I think that s the stage we re at in these biochemical speculations There has been no demonstration to my knowledge of any major abnormality of the biochemistry of the human hypertensive unless it is in the production of some of these pressor agents

DR SEVEN I think that we re at the beginning of a new phase in the analysis of trace metals in various diseases and I would like to point out that methodology is extremely important in this field The study of the urinary output of various ions or of plasma levels is a deductive process We might deduce something from these levels about a biochemical process To set up a determination for a single element, one has to work in an atmosphere in which everything is trace metal free Then you have the problem of continual contamination by reagents The colorimetric reagents if you are using them are often not specific So it is a very very difficult process and one that is going to take a lot of time

DR SCHROEDER I have noticed in Dr Seven s presentation and again here a couple of comments about our methods I agree entirely with what he said The methods are extremely difficult Dr Perry is an excellent biochemist and has been able to conquer them And I think to a large measure it is not a deductive process These are quantitative measurements plus or minus 5 per cent in some metals less in others and about 10 per cent in others Now as far as time is concerned Dr Perry and his wife who helped him spend 12 hours to do one urine To collect the urines on a number of patients requires hours of steady work I do rely expressly on these results Other people who have seen his methods which are based on a method of salt analysis that has been developed in England consider it accurate

DR. SEVEN I was referring in part to some of the data you have reported Dr Schroeder The problem was that I was unable to find the methods published Have they been published so that other people might look at them or use them?

DR. SCHROEDER I think they re in press at the moment

DR. CORCORAN I ve got one question I d like to ask Dr Wakerlin There

has been proposed the concept that in renal hypertension due to partial arterial occlusion a shift in mechanisms occurs The mechanism is initially humoral but after some months there is a change in the set of the buffer nerves and receptors If you now remove the kidney the hypertension tends to persist This is a function of time McCubbin and Page have some data bearing on this it occurs within weeks and not a matter of months or years Therefore I wondered about one of your slides Dr Wakerlin You injected antirenin into a dog that had renal hypertension I think the slide said 103 months which is quite a long time and the high blood pressure promptly came down This is inconsistent This dog for example is an exception possibly and didn t shift his buffer mechanism or do you think there is a prolonged acting humoral factor in renal hypertension?

DR WAKERLIN That s a very good question Dr Corcoran We have a number of dogs I should say a total of some 40 or 50 dogs with hypertension of more than 4 years duration all of which have shown reductions in blood pressure on active immunization and also on passive transfer so that this is not a unique experience for this particular dog I wonder if these results can t be reconciled by the concept that in the chronic hypertensive animal renin may come to have an action intrarenal in character whereby it reduces the blood pressure regulatory function of the kidney that Dr Grollman talks about This would bring these two concepts into line and would explain the fact that when you take the kidneys out of an animal if it has had hyper tension for a period of time the blood pressure does not come down acutely and then perhaps goes up later on the basis of a renal mechanism This is the only explanation I have for this inconsistency

DR CORCORAN The dog s buffer nerve system is not the only thing holding the blood pressure up in the chronic renal hypertensive dog This should give our Chairman a chance to say something about his own observations

DR GROLLMAN The lateness of the hour requires that I forego saying anything about my own work It is obvious that there is still much to be done in this field There has been much said with which I would heartily disagree However the mere fact that there is this great disagreement should console those who are confused at the end of this discussion In conclusion I would like to thank the members of the panel for their help and the audience for their patience

The Adrenal Cortex in Hypertension (With Particular Reference to Adrenal Regeneration Hypertension)

R GAUNT F GROSS A A RENZI and J J CHART

Research Departments CIBA Pharmaceutical Products Inc Summit N J and CIBA Limited Basle Switzerland

The subject of this paper involves a vast literature confused and conflicting in some respects but nevertheless containing a large body of established information Unfortunately however this wealth of information has not led to satisfactory generalizations concerning the role of the adrenal cortex in the more common types of hypertension This paper outlines some of the evidence that seems to associate the adrenal cortex with hypertensive disease and deals particularly with the experimental syndrome known as adrenal regeneration hypertension

EVIDENCE RELATING THE ADRENAL CORTEX TO HYPERTENSION

Adrenalectomy causes a reduction in blood pressure from normal levels beginning within a few hours after operation[1] before any gross aspect of adrenal insufficiency is apparent Replacement therapy as far as the maintenance of blood pressure is concerned can be effected with either the so called mineralocorticoids or glucocorticoids The former are more effective in chronic use for the maintenance of blood pressure under ordinary conditions the latter are far superior in preventing the circulatory collapse under stressful conditions to which adrenal deficient subjects are particularly susceptible Thus we have here the suggestion to be amplified later that different corticoids affect blood pressure in different ways

The Adrenal in the Maintenance of Hypertensive States This is inevitably a complex problem because of questions of specificity of action Adrenalectomy will in most cases eventually abolish hypertension if for no other reason than that it abolishes life itself Nevertheless the problem has been studied in meaningful ways in many types of experimental hypertension since Goldblatt s demonstration that the adrenal cortex but not the medulla was necessary for the maintenance of renal hypertension The adrenal is not essential for metacorticoid[3,4] or salt hypertension[5,6] In most other types however something more than a minimal life maintaining amount of corticoid is required to maintain hypertension [13] The corticoids have some role in maintaining high blood pressure suggestive at least of permissive[13] if not causal actions

The Adrenal and Responsiveness to Pressor Agents Another aspect of the problem of uncertain but highly suggestive significance is that in

acute tests adrenalectomy tends to reduce and corticoid overdosage to enhance the responsiveness to numerous but perhaps not all pressor influences[14, 19] For instance in the rat desoxycorticosterone and salt increase sensitivity to epinephrine norepinephrine renin hypertensin and vasopressin [1] Adrenalectomy reduced either the intensity or duration of response to some but not all of these agents In addition the corticoids affect the reactivity of mesenteric blood vessels as determined by direct observation [6]

In animals conditioned by steroids and salt renin causes widespread vascular damage massive ascites and death—the so called eclampsia like syndrome—a pattern of effect entirely different from that seen when renin was given normal animals[23]

This "conditioning effect of corticoids and the opposite effect of their lack could be a factor of great importance in cardiovascular disease but is one inherently difficult to evaluate in clinical circumstances

Steroid Overdosage Hypertension

Excesses of most or possibly all of the biologically active steroids have pressor actions[8] and when given chronically cause hypertension—if test species and conditions are properly selected It is not clear however that all of these steroids act by the same mechanism indeed there is reason to think they do not

Desoxycorticosterone The desoxycorticosterone hypertensive syndrome has usually been studied in rats and following Selye Hall and Rowley [6] is usually produced by large doses of the steroid in animals conditioned by the removal of one kidney and by a high salt intake It is characterized by hypertension nephrosclerosis cardiac hypertrophy and widespread vascular damage The syndrome is a malignant one but animals can be protected with antihypertensive drugs[27] Other species do not necessarily respond in the same way In man however an adrenal enzyme deficiency resulting in excess mineralocorticoid secretion is associated with hypertension [9] The desoxycorticosterone syndrome becomes after a time irreversible i e it continues after the administration of steroid and extra salt are discontinued[29, 3] This permanent state has been called *metacorticoid hypertension* Since the original work of the Selye group it has been widely confirmed that the ability of desoxycorticosterone to produce hypertensive disease is facilitated by a high salt intake and abolished by severe salt restriction[30] The ability of the steroid to deplete renal pressor substances is also dependent on dietary salt Desoxycorticosterone causes sodium accumulation and potassium depletion in various tissues including arterial walls[31, 3] and changes in kidney function relative to the handling of sodium loads[33, 34] Some of these actions are not specific for desoxycorticosterone hypertension as contrasted with other types of hypertension and cause and effect relationships are obscure

Relation of Desoxycorticosterone Hypertension to Renal Hypertension Although desoxycorticosterone hypertension is associated with renal hypertrophy nephrosclerosis and other kinds of kidney damage the syndrome is not the same as that of renal hypertension Desoxycorticosterone can elevate blood pressure before discernible kidney pathology is apparent and will exert its characteristic action in the absence of kidneys[3, 37] The difference between the abilities of transplanted kidneys from metacorticoid and

renal hypertensive rats to lower blood pressure in renal hypertension sharply distinguishes between the status of kidneys in the two types of hypertension [33] In addition, arteriolar pharmacologic reactions are distinctly different in desoxycorticosterone and renal hypertension [39]

Relation of Adrenal to Renal Pressor Agents The corticoids (at least desoxycorticosterone) reduce the content of renin or renin like substances in the kidney even under circumstances in which hypertension does not occur [40] desoxycorticosterone also causes degranulation of the cells of the juxtaglomerular apparatus [40 4 88] The similar depletion of renin in intact kidneys after unilateral renal ligation is prevented by adrenalectomy and restored after adrenalectomy by large doses of desoxycorticosterone but not by small doses of either desoxycorticosterone or hydrocortisone [11 1] This and related evidence suggest but do not prove that renin may stimulate either directly or indirectly the secretion of aldosterone or related steroids [13 40] The relation of these events to the actual cause of hypertension however is obscure since like the effects of corticoids on plasma renin and hypertensinogen levels [43 46] they cannot be closely correlated with changes in blood pressure They serve nevertheless again to implicate the adrenal at least by association with hypertensive processes

Aldosterone If there is a corticoid widely involved in causing hypertension current suspicion points first to aldosterone because it is the major natural mineralocorticoid and hypertension is present in most of the known cases of primary aldosteronism [47 48] Genest s group[49] particularly has advanced the hypothesis that a mild chronic aldosteronism is a major cause of essential hypertension This hypothesis is difficult to prove because of difficulties of measuring a mild aldosteronism and eliminating such variables in its production as changing sodium intake Therefore final judgment must await more definitive evidence

Experimentally however it is clear that if aldosterone like many other steroids is given in large enough dosage together with salt it will cause hypertension [50] Relative to desoxycorticosterone however it takes large doses in terms of sodium retaining and life maintaining potency There has been lack of consistency of results when small doses of aldosterone were given for long periods Gross *et al* [1] and Gaunt *et al* found no effects while Kumar *et al* [3] reported hypertensive effects

The Glucocorticoids In addition to desoxycorticosterone and aldosterone hypertension can be induced by cortisone [54] hydrocortisone [56] 17 desoxyhydrocortisone (Compound S) [57] corticosterone[58] (Gross unpublished) and by numerous synthetic analogs [9] of the natural corticoids The hypertension caused in animals by cortisone or hydrocortisone however differs from that caused by desoxycorticosterone in various respects [60] including the following (a) it is not dependent on dietary sodium and may be enhanced by sodium restriction [54 61] (b) it involves no serum electrolyte changes [4] (c) there is little or no histologic evidence of renal or vascular damage [4] (d) serum cholesterol levels are elevated [54] (e) the hypertension is not intensified by either uninephrectomy or saline [6] (f) in severe potassium depletion cortisone causes hypertension while desoxycorticosterone will not [62] (g) hypertension develops faster than with desoxycorticosterone but is of lesser magnitude [63] (h) the hypertension is easier to control by drugs than that caused by desoxycorticosterone [64]

The absence of renal and vascular damage might be expected because of the anti inflammatory connective tissue inhibiting properties of the gluco corticoids The fact however that the glucocorticoids act independently of the sodium ion indicates a fundamentally different type of action Such differences might have been anticipated from their different actions as replacement agents in adrenal insufficiency

ADRENAL REGENERATION HYPERTENSION

In 1955 Skelton[6] discovered a type of hypertension of intriguing interest If a rat's adrenal is nicked and the medulla and most of the cortex squeezed out a new cortex promptly regenerates from the remaining capsule and adjacent cells There is some lack of agreement as to the functional capacity of such regenerating glands[66 67] but our early experiments clearly suggested that they were hypofunctional[68] Skelton found nevertheless that if animals with a regenerating gland (the second adrenal being removed) were sensitized by the removal of one kidney and the feeding of a high salt diet a severe hypertension develops

This phenomenon is of interest because we are dealing with a disturbance in endogenous adrenal function which in the presence of known and readily controlled sensitizing procedures causes hypertension If the process were understood thoroughly it might provide important clues as to the role of the adrenal in hypertensive disease While no certain sequence of cause and effect events has yet been established some important facts and implication are available (a) The syndrome looks like a milder version of desoxycorti costerone hypertension—one in which blood pressure is a little less high and tissue pathology milder but of the same time[69] This includes a hyper sensitivity to the vasculotoxic action of renin [0] and a diminution of the pressor substance in the kidney (Gross unpublished) (b) Like desoxycorti costerone hypertension it is salt dependent but unlike desoxycorticosterone hypertension is wholly dependent on unilateral nephrectomy[71] (c) There are apparent colony differences or some unrecognized environmental variables that make the syndrome hard to produce or variable in its manifestations in some laboratories (personal communications) (d) Young rats are apparently more susceptible than adults but in our colony hypertension can be produced at various ages and as Skelton [1] and Masson and Corcoran [5] found in both sexes Neff and Correll [3] find however that females are much more susceptible than males

Pharmacologic Studies One way to characterize an experimental disease is in terms of its response to pharmacologic agents and that has been one of our major interests in this case Neff and Correll[73] found that testosterone given female rat at the time of adrenal enucleation would prevent hypertension from occurring Skelton *et al*[74] found that stilbestrol would do the same thing On the other hand Masson and Corcoran found no effect of either estrogens or androgens

We have observed that 1 dehydro-17α methyl testosterone a steroid with very little androgenic or estrogenic activity had a distinct protective influence (Fig 1) This compound inhibited adrenal regeneration to some degree and also reduced the salt appetite (Fig 1) Its protective action could have been due to either or both of these factors It does not

however have corticoid action *per se* nor does it cause adrenal atrophy in intact animals or inhibit compensatory adrenal hypertrophy If it has ACTH inhibiting actions therefore which account for the effects observed here these are manifest only under some special circumstances Interestingly enough this same steroid inhibits renal (H Bein personal communication) but not desoxycorticosterone hypertension (Gross unpublished)

Treatment with corticoids like that with sex hormones has presented a varying pattern of responses probably dependent primarily on their varying abilities to inhibit adrenal regeneration (*i e* inhibit ACTH output) and themselves to cause hypertension directly In our hands hydrocortisone

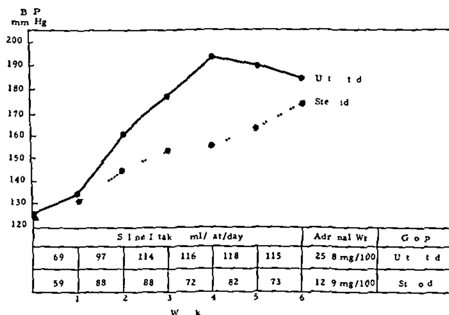


Fig 1 Effect of a steroid with weak sex hormone like activity on adrenal regeneration hypertension Kidney heart and brain weights were lower in steroid treated group Mean data are on 6 female rats per group

in doses which caused slight (0 1 mg /day) or marked (1 0 mg /day) inhibition of regeneration did not prevent hypertension although it may have altered its typical pattern of development Although hydrocortisone can itself cause hypertension it will not usually do so in the doses we used That delicately balanced factors are involved is shown by Skelton s demonstration [8] that 1 mg /day of corticosterone partially suppresses adrenal regeneration and also *prevents* hypertension 5 mg doses completely suppressed regeneration and *caused* severe hypertension Subsequently Grollman [6] also found that a certain combination of cortisone and desoxycorticosterone acetate prevented adrenal regeneration hypertension

Nonsteroidal Drugs We have found adrenal regeneration hypertension to be an interesting and apparently useful tool in studying miscellaneous

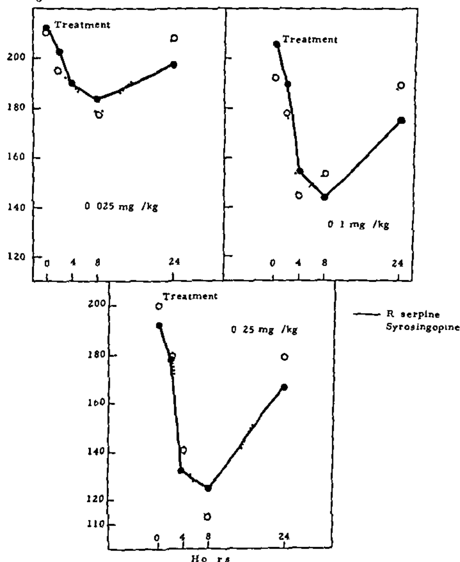


Fig 2 The acute effects of single equal doses of reserpine and syrosingopine on blood pressure in adrenal regeneration hypertension Despite the markedly reduced sedative activity of syrosingopine relative to reserpine the two drugs had equal effects on blood pressure and effects which were proportional to dosage Curves are based upon means of 6 to 20 rats per group

hypotensive drugs In acute single dose experiments it responds exceedingly well to reserpine and to its synthetic derivative syrosingopine (carbethoxysyringate ester of methyl reserpate Singoserp) The latter is virtually without sedative action in the rat but the equal hypotensive effects of the two at various dose levels are shown in Figure 2 In chronic experiments syrosingopine can be given at doses much higher than those tolerated with reserpine with corresponding greater effect on hypertension (Figs 3

and 4) One but not the only means of protective action of reserpine in this sort of situation is to reduce the spontaneous intake of saline drinking solution [75] Syrosingopine has this property to some degree but less than reserpine Certainly its action in acute experiments is not due to this cause In addition it reduces blood pressure in hydrocortisone induced hypertension (Fig. 5) a condition not dependent on a high salt intake and one previously found to be highly responsive to drug therapy [64]

A different pattern of response is seen if one studies the effects of the antihypertensive diuretic agents Sturtevant and Hansen[77] found some action of various diuretics in desoxycorticosterone and metacorticoid hypertension

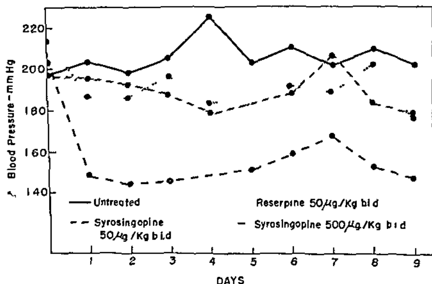
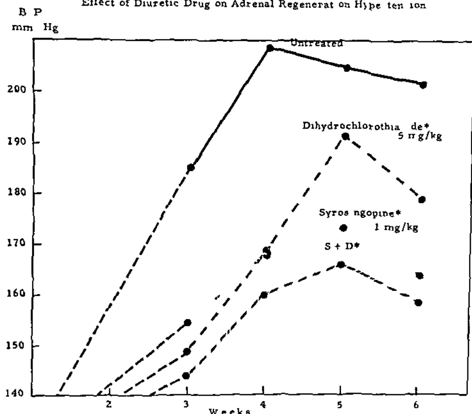


Fig 3 Equal effects of equal doses of reserpine and syrosingopine on established adrenal regeneration hypertension Animals could not tolerate reserpine in amounts equal to the high doses of syrosingopine used Curves based on 6 to 12 rats per group Compare with Figure 4 and reference No 75 which show effects of these drugs when treatment begins before hypertension is established Pressures were taken before maximal effect of morning treatment in each case which presumably accounts for the lesser effects than those observed in acute responses shown in Figure 2

sion We have studied recently hydrochlorothiazide a compound more potent than chlorothiazide as a diuretic This drug did not affect hydrocortisone hypertension (Fig 5) a syndrome as noted above not dependent on sodium intake nor did it have effects on adrenal regeneration hypertension when given acutely It did however reduce salt intake and ameliorate adrenal regeneration hypertension when given chronically (Fig 4) We presume in view of these circumstances that unlike the reserpine derivatives its only protective action was that exerted in some fashion on sodium metabolism

We have found that adrenal regeneration hypertension like desoxycorticosterone hypertension cannot be well controlled with ganglionic blockers One is thus reminded of Schroeder and Davies generalization in 1954[78]



Average Da ly 1% Salin Intake ml					Adrenal Wt mg /100g
U t eated	72	81	83	80	18 3
*** Syr singop ne	74	88	68	60	15 9
* D hydro hlo othiaz de	57	60	52	52	16 5
** S + D	58	69	72	65	15 9

* D ff r nt from untr at d, P < 01
** D ffe ent from unt eated P < 02
*** ? from unt eated P > 05

Fig 4 Effects of daily treatment with dihydrochlorothiazide and syrosingopine singly and combined on adrenal regeneration hypertension Dihydrochlorothiazide was given in the drinking water at a dose approximating 5 mg /kg /day One mg /kg of syrosingopine was divided into two subcutaneous doses Brain heart and kidney weights were less in all treated than in untreated groups

that the humoral hypertensions are relatively unresponsive to ganglionic blockers

Cause of Adrenal Regeneration Hypertension It was widely postulated at first that adrenal regeneration hypertension was due to an excess production of aldosterone or some other corticoid Subsequent work has produced no definite evidence favoring that view and considerable against it As mentioned above older indirect evidence indicated that regenerating adre

nals were hypofunctional More recently two more definitive studies have been made In one steroid production was studied in incubated regenerating adrenals with and without added ACTH, in the other the effluent from cannulated adrenal veins was analyzed (Pellegrino and Brogi of Pisa personal communication) Both studies indicated that regenerating glands secreted subnormal amounts of steroids measured including aldosterone and corticosterone and provided no evidence for disturbed ratios of secretory products The possibility that some unknown pressor steroid is secreted in excess has not been eliminated but seems remote

If nothing is produced in excess then could there be a failure to secrete

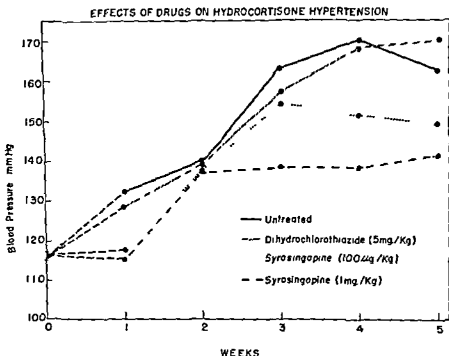


Fig 5 Effects of daily treatment with dihydrochlorothiazide and syrosingopine on hydrocortisone induced hypertension The rats were adrenalectomized and received 2 mg hydrocortisone acetate per day They did not receive extra salt 4 to 5 rats/group

some specific substance that prevents hypertension? No evidence direct or indirect supports such a view However in a related vein Masson *et al* suggest that in the presence of the proper sensitizing procedures a mild adrenal insufficiency may serve to facilitate the development of hypertension Such a concept may receive at least oblique support from numerous reports that exogenous steroids cause hypertension more readily in adrenalectomized animals and Addisonian patients than in normal ones (e g Perera [9]) and that whole adrenal extracts inhibit the pressor actions of desoxycorticosterone [61, 6] In view of all known facts about corticoid function this theory rubs intuition the wrong way it would be more satisfactory to have a positive explanation for a positive event Rats however have little urge to honor human intuition and Masson's theory at the present time will

explain more facts than any other It is consistent with some of Skelton's[38] observations has been supported by Grollman [6] and seems best to explain a series of our experiments in which regenerating adrenals were transplanted to various sites

The basis of this latter work was our old observation[68] that enucleate adrenals had different functional capacities at different transplantation sites The kidney and ovary were excellent sites as judged by the functional performance of the transplanted gland Muscle was a poor one The intestinal mesentery was also not a good site but we judged this to be due to the fact that much of the corticoid was inactivated by going to the liver before it got to the rest of the body inasmuch as pellets of pure steroid were also "weaker" at sites with hepatic portal drainage

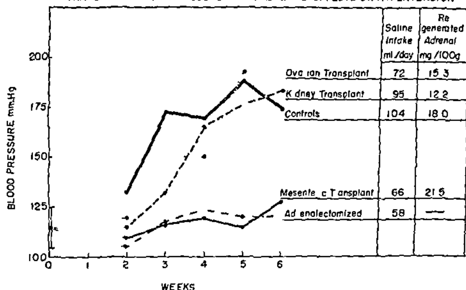


Fig 6 Effects of transplanted regenerating adrenals on hypertension Controls were subjected to the standard Skelton procedure unilateral adrenalectomy and nephrectomy plus enucleation of the remaining adrenal and 1 per cent NaCl solution as drinking fluid Except for transplantation of the enucleate gland or total adrenalectomy other groups were treated similarly 6 to 11 animals/group

In our new experiments[83] it was found that regenerating glands transplanted to the kidney or ovary caused hypertension with a probable slight lag in onset almost as readily as those *in situ* (Fig 6) Transplants to the mesentery failed to cause hypertension and after saline was withdrawn maintained life but failed to support normal growth thus indicating suboptimal functional capacity (Figs 6 and 7) Totally adrenalectomized animals did not get hypertension and most of them died after saline supplements were withdrawn e g showed total adrenal insufficiency (Figs 6 and 7) We interpret this to mean that the partially deficient adrenal function in the animals with regenerating glands *in situ* or transplanted to the ovary or kidney predisposes to hypertension Some critical amounts of corticoids are however, required to cause hypertension—an amount not available from

transplants to the mesentery because of hepatic inactivation and of course not available in the adrenalectomized animals (The variable salt intakes of these different groups [Fig 6] together with data on drugs cited above suggests that almost any influence which reduces blood pressure reduces salt appetite The effect of hydralazine is an exception to this rule[75])

In any case it seems to be true that either a partial deficiency or an excess of corticoids other conditioning circumstances being favorable promotes hypertension If this is the case it opens wide avenues of possible adrenal cortical participation in hypertensive disease which have been little studied or even considered One of the greatest barriers hitherto to considering the adrenal cortex of importance in the etiology of common types

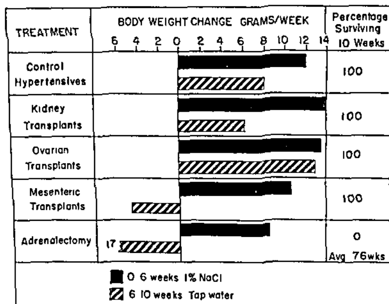


Fig 7 Same groups as shown in Figure 6 showing survival and weight changes while receiving and later while not receiving 1 per cent NaCl to drink The different growth rates under the various conditions are presumably rough indices of the functional capacity of the transplanted glands

of hypertension was the failure to demonstrate by convincing criteria the presence of adrenal hyperfunction Perhaps we should look with equal intensity for some altered or even deficient function

CONCLUSIONS

Perera[80] has written Beyond doubt the adrenal cortex plays a part in the regulation of blood pressure Beyond doubt the mechanisms involved are complex and not due to direct humoral action inasmuch as changes in arterial tension require days not minutes and are scarcely proportional to dosage The simplest situation namely that the adrenal cortex secretes an excess of pressor corticoids which by direct or indirect means cause hypertension has been demonstrated convincingly as yet only in a limited number

of cases of overt adrenal disease New suggestive evidence which may lead to revision of this statement is becoming available[84]

It is however clearly established that (a) the corticoids have a supporting role in normotension and in the maintenance of various kinds of hypertension (b) all known biologically active corticoids can under certain conditions cause hypertension (c) the different corticoids achieve this end in different ways—the mineralocorticoids but not the glucocorticoids requiring the sodium ion and causing widespread vascular and renal damage (d) the absence of corticoids diminishes or abolishes and an excess enhances the responsiveness to a wide variety of pressor influences

It is clear also that the corticoids have *some intimate but still ill defined* relation to the renal pressor depressor mechanisms specifically to the content of renin in the kidney Possibly renin serves directly or indirectly to stimulate the secretion of aldosterone To confound a confused situation *further there are experimental and probably clinical conditions in which* either an *excess* or *deficiency* of corticoids may favor the hypertensive process In addition for the corticoids to be causally related to hypertension it may not be required that they be secreted in abnormal amounts either in terms of excess deficiency or abnormal ratios There are numerous circumstances e g renal disease[85 86 13] altered electrolyte metabolism altered hormone balance (relative excess of growth hormone?) in which sensitivity to corticoids may conceivably be so altered as to change the normal role of a normal amount of corticoid into that of a pathogenetic agent

We think these possibilities should be taken seriously but in calling attention to them we realize that we have to a considerable degree only built a complex hypothetical house of cards By analogy we can say that the adrenal cortex is like a lady who has kept bad company and late hours for so long that human nature being what it is she must have sinned Testimony has been brought against her however only by her few suitors who had adrenal hyperplasia or adrenal tumors Her other friends have refrained from talking Perhaps this is because they are gentlemen or perhaps it is only that they do not have much to talk about

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Clinical Observations on the General Effects of Steroids and the Adrenal Cortex on Blood Pressure and the Relationship to Hypertension

LEWIS C MILLS
Hahnemann Medical College and Hospital

As with fever and many other manifestations of disease states hypertension may be due to one or a combination of etiologic agents In some instances as is true in patients with pheochromocytoma the etiologic mechanism is well understood in others and especially essential hypertension possible mechanisms have been proposed but have not yet been clearly established In these latter instances experimental and clinical observations suggest that adrenal cortical hormones may be intimately connected with the pathogenesis of hypertension and it is certain that such hormones if not directly involved are necessary or exert a "permissive" action in its development and maintenance

The evidence which suggests that adrenal cortical hormones may be a primary etiologic factor in some types of hypertension is steadily increasing Such a relationship was perhaps first suspected when hypertension was noted to be one of the major manifestations of Cushing s syndrome This observation was reinforced when desoxycorticosterone acetate (DCA) was noted to increase blood pressure to normal in patients with Addison s disease and that further increases in dosage in such patients often led to the development of hypertension In animal experiments using appropriate accompanying conditions administration of DCA leads to development of severe hypertension and cardiovascular renal disease The pharmacologic use of cortisone hydrocortisone prednisone and 9α fluorohydrocortisone as well as many other synthetic steroids is associated with the development of hypertension in a significant number of patients Other evidences which suggest adrenal participation are the occurrence of hypertension in certain patients with congenital adrenal hyperplasia its occurrence in certain animals after adrenal enucleation during the phase of adrenal regeneration the possible relationship of hypertension to stress and the adaptation syndrome the finding in some patients and animals of electrolyte alterations of the type commonly resulting from large doses of adrenal steroids the hypotensive effect of certain drugs which block the electrolyte effects of adrenal steroids and the frequent occurrence of clinical syndromes which while not classical of Cushing s syndrome are characterized by hypertension plus varying combinations of obesity diabetes hirsutism and menstrual disturbances suggestive of adrenal dysfunction In addition adrenalectomy has been shown to lower blood pressure significantly in a large percentage of hypertensive patients

CUSHING S SYNDROME

Hypertension is a common finding in Cushing s syndrome being present to some degree in as many as 85 per cent of patients When adrenalectomy is done early in the course of the disease arterial blood pressure often returns to normal and remains at this level even though adequate replacement therapy with hydrocortisone and desoxycorticosterone acetate is given In those patients with a more advanced state of disease in whom vascular and renal deterioration has occurred this procedure may have little effect on the hypertension but undoubtedly secondary factors such as pressor agents from the damaged kidney are responsible for maintenance of elevated blood pressure in this phase of the disease In Cushing s syndrome the evidence seems clear cut that the primary etiologic factor in the hypertension is excessive or unbalanced adrenal cortical secretion On the other hand it is difficult to determine the exact steroidal abnormality responsible for the hypertension It is known that secretion of hydrocortisone is increased Other steroids such as 17 ketosteroids and estrogens are also found to be variably increased Genest *et al*[1] reported aldosterone to be markedly increased in one hypertensive patient with Cushing s syndrome the daily excretion ranging from 32 to 210 micrograms per day (normal values for this method are 1 0 to 9 5 mcg) Another patient who was normotensive excreted 5 3 micrograms per day however a third patient with moderate hypertension also had normal values of 3 5 and 5 0 micrograms per day

CONGENITAL ADRENAL HYPERPLASIA

In patients with congenital adrenal hyperplasia it is well known that associated with the clinical picture of female pseudohermaphrodism and macrogenitosomia praecox there may be a salt losing syndrome or a hyper tensive syndrome In Wilkins series five patients with congenital adrenal hyperplasia were hypertensive In all of these blood pressure returned to normal during therapy with cortisone In one patient blood pressure be came elevated with cessation of therapy and again returned to normal when cortisone was reinstituted In these patients as in Cushings syndrome hypertension is due to adrenal cortical secretory abnormalities A possible mechanism for this was elucidated by Eberlein and Bongiovanni[3] who studied the urinary steroid excretion pattern in one patient who had severe hypertension in association with congenital adrenal hyperplasia In this patient 11 oxygenated steroids were undetectable and the predominant C 21 steroids were tetrahydro 11 desoxycortisol tetrahydro desoxycorticos terone pregnanetetrol and pregnanetriol Large amounts of etiocholanolone and androsterone were also present Since 11 desoxycortisol has minimal if any hypertensive effects it was postulated that excessive secretion of desoxycorticosterone was the most likely explanation of the hypertension and that this resulted from a lack of adrenal cortical 11 β hydroxylase In other patients with congenital adrenal hyperplasia there seems to be a greater deficiency of 21 hydroxylase than of 11 β hydroxylase[4] with the resultant effect that production of salt retaining substances may be dimin ished in some patients this becomes of sufficient magnitude to result in a salt losing syndrome with hypotension

PRIMARY ALDOSTERONISM

Primary aldosteronism is due to excessive secretion of aldosterone by the adrenal cortex the most common pathologic lesion being a benign adenoma (90 per cent) *In approximately fifty patients mentioned by* Conn[5] the majority had hypertension In many of these aldosterone has been shown to be the only steroid present in excessive amounts Removal of the tumor is associated with a return to the normotensive state in most but not all of these patients Even though hypertension continues in a few patients the significance of these observations is not lessened since it is likely that those patients not having a hypotensive response after adrenalectomy had devel oped secondary renal disease (hypokalemic nephrosis) pyelonephritis or *perhaps a situation analogous to experimental* DCA hypertension in which hypertension is permanent if DCA therapy is continued beyond a critical period of time

In spite of these results it is somewhat disturbing to note that patients with familial periodic paralysis (intermittent aldosteronism) do not have hypertension[5] but it is possible that chronic elevation of circulating aldo sterone with secondary renal disease is necessary for the development of severe hypertension

OTHER TYPES OF ADRENAL CORTICAL HYPERSECRETORY STATES

Hypertension is uncommon in other types of adrenal cortical hyper

secretory states In purely masculinizing syndromes (adrenogenital syndromes in adults) and in patients with feminizing adrenal cortical carcinomas elevation of blood pressure is not common These observations suggest that adrenal androgens and estrogens do not play a major role in the development of hypertensive states

In addition to these syndromes there are less well defined conditions characterized by Schroeder and Davies as endocrine hypertensive syndromes "[6] In an analysis of female patients with hypertension in their clinic about 20 per cent were found to have in addition to hypertension features suggestive of an endocrine disorder which could be related to possible adrenal or gonadal disturbances Their symptoms and signs included sudden weight gain prior to the onset of the hypertension development of central obesity and buffalo hump reproductive disturbances (most commonly irregular menses—74 per cent) a tendency to ecchymoses—60 per cent hirsutism—40 per cent tendency to edema—40 per cent abnormal carbohydrate tolerance—25 per cent and acne—21 per cent "If all of the findings in these women were consolidated into one case that case would have Cushing's syndrome without osteoporosis Some confirmation was lent to the diagnosis by the finding of adenomata or focal hyperplasia of the adrenal cortex in every one of seven patients in whom it was possible to examine the adrenal glands

ADMINISTRATION OF STEROIDS

Administration of certain adrenal cortical steroids to humans and animals leads to the development of hypertension In normal rats desoxycorticosterone acetate produces mild hypertension If rats are "sensitized by unilateral nephrectomy and sodium chloride is added to their drinking water severe hypertension and later severe vascular disease result It should be noted that this is reversible in the early phases if therapy is stopped but becomes permanent if vascular disease and renal deterioration are permitted to develop In normal humans DCA usually has little effect on blood pressure[7] even in relatively large doses as compared to those required for maintenance of an Addisonian patient but again, as in animals if sodium intake is excessive or renal disease is present the blood pressure effects are potentiated On the other hand in patients with adrenal insufficiency it is quite easy to produce hypertension with DCA suggesting that in the normal individual certain adrenal steroids may have an antagonistic effect to DCA and that the resultant hypertension in patients with Addison's disease is due to the deficiency of steroids having an antagonistic action to DCA rather than the absolute level of desoxycorticosterone alone DCA is also pressor in hypertensive dogs[8] and in hypertensive patients [7]

Normotensive patients receiving large doses of cortisone and ACTH frequently develop hypertension [9] Similar results have been observed with hydrocortisone prednisone prednisolone 9α fluorohydrocortisone and other synthetic steroids with mineralocorticoid activity The incidence of hypertension can usually be correlated with dosage but not necessarily with sodium retaining potency For example the incidence of hypertension is approximately the same from hydrocortisone and prednisone when equivalent anti inflammatory doses are used even though at these dose levels sodium retention is greater with hydrocortisone In contrast administration

of ACTH or cortisone to hypertensive patients may not lead to further elevation of blood pressure[10] and it has been reported that in occasional patients blood pressure may decline toward normal during administration of cortisone[11, 12]

Administration of aldosterone to normal subjects has led to some increase in blood pressure however in two subjects large doses (3 mg and 6 mg/day for 14 and 22 days respectively) elevated the diastolic pressure only 10 to 20 mm of mercury[13] This seems analogous to the situation in familial periodic paralysis and it is possible that a longer course of treatment might have led to a greater rise in blood pressure

STEROID EXCRETION IN PATIENTS WITH ESSENTIAL OR RENAL HYPERTENSION

Reports concerning steroid excretion in essential and renal hypertension have been variable and conflicting Genest[14] studied seven patients with essential hypertension for periods of two to seven months under conditions of high and low sodium intakes Although seven different chromatographic fractions of urinary steroids were examined there was no distinct abnormality in steroid excretion During severe sodium restriction five of the patients became normotensive Repetition of steroid analyses at this time revealed no significant change in the excretion pattern Tobian[1] found normal formaldehydogenic steroids in eight of nine patients with essential hypertension and Daughaday[16] in three patients In contrast Corcoran *et al*[17] noted increased levels in twenty of forty six patients in patients in whom four or more determinations were done urinary formaldehydogenic steroids were elevated in nine of ten Bioassays of urinary corticoids have also shown increases in some patients with hypertension[18]

In a series of sixteen women from the Hahnemann Hospital Hypertensive Clinic the mean urinary excretion of 17 hydroxycorticoids and 17 ketosteroids was not significantly different from that of nonhypertensive patients however because of possible variables in race sex age concurrent disease duration and type of hypertension a much larger series will be necessary to determine whether there are differences in steroid excretion in these two groups of patients Since steroidal imbalance may be important determinations of various classes of steroids should be done simultaneously

Venning *et al*[19] measured the excretion of free and conjugated formaldehydogenic steroids glucocorticoids and sodium retaining factor" in normal pregnant women in toxemia of pregnancy and in hypertension of pregnancy without toxemia Glucocorticoids were lower than normal in toxemia sodium retaining factor and free and conjugated formaldehydogenic steroids were increased in toxemia and in the hypertensives with the exception that conjugated formaldehydogenic steroids were less than normal in patients with severe toxemia

Genest *et al*[1, 20] measured excretion of aldosterone in normal controls and in fifty four patients with essential malignant and renal hypertension The mean excretion of the hypertensive group was approximately two times normal 55 per cent of this group having levels above normal or in the high normal range Marked fluctuations in aldosterone excretion were found in three patients in whom serial determinations were done this also being in contrast to the normotensive subjects In three patients with hypertension

due to coarctation of the aorta excretion of aldosterone was within normal limits It should be noted that these studies did not determine whether the increased aldosterone excretion was primary or secondary and while the data from patients with coarctation suggests that it is not due to the hypertension *per se* in the hypertension of coarctation the adrenals kidneys and liver are not subjected to the effects of the elevated blood pressure and the adrenal response could well be modified

Steroid formation by adrenal tissue from normotensive patients and those with hypertension has been studied *in vitro* Cooper *et al* [1] found a negative correlation between steroid formation per gram of adrenal cortical tissue and diastolic blood pressure However this was associated with a fall in the ratio of hydrocortisone/corticosterone because formation of corticosterone declined less rapidly than hydrocortisone with increasing levels of diastolic blood pressure In spite of this the rate of formation of all steroids measured except 11 β hydroxyandrostene-3 17 dione was doubled in the less severe hypertensive group as compared with the normotensive group There was a positive correlation between adrenal weight and diastolic blood pressure It was thought by these authors that the finding of decreased hydrocortisone in relation to corticosterone suggested a possible deficiency of adrenal 17 hydroxylase

PATHOLOGY OF THE ADRENAL CORTEX IN HYPERTENSION

The pathologic appearance of the adrenal cortex in patients with hypertension has been reported by several authors [6] [1 2] [23] [4] [5] Although the cortex appears to be normal in some patients pathologic lesions are frequently found Etienne Martin [6] noted lymphocytic islets (73 per cent) muscular hyperplasia of the central adrenal vein (73 per cent) spongiocytic hyperplasia (89 per cent) fibrosis of the capsule with arteriolitis and hyalinization (63 per cent) and loss or fibrosis of the zona glomerulosa (59 per cent) in the adrenal glands of patients with hypertension The adrenals may be increased in weight and this has been correlated with diastolic blood pressure [1] Areas of nodular hyperplasia focal adenomas and arteriolosclerosis of adrenal vessels may be present [6] [1] [3] Russi observed 131 instances of adrenal adenoma in the records of 9000 autopsies [4] Hypertension was five times more common in this group than in those without adenomas The adenomatous group was further characterized by having less arterial nephrosclerosis than the hypertensive patients without adenomas suggesting that the hypertension may have had a different etiology

Although renal vascular involvement was less in Russi s patients steroid hypertension may be associated with severe vascular disease Experimentally the severity and incidence varies with the steroid used chronic DCA administration being associated with severe vascular disease [7] In contrast the pathologic change due to DCA in dogs can be prevented by administration of adrenal cortical extract [8] and vascular disease is less severe when hypertension is induced by cortisone [7 9]

POSSIBLE MECHANISMS OF STEROID HYPERTENSION

The exact pathogenesis of steroid induced hypertension is unknown although several possibilities have been suggested Since hypertension may be

induced experimentally by adding saline to the drinking water of rats[30] and since steroids may lead to salt retention it has been suggested that this is a likely mechanism

Albert *et al*[31] have observed significantly higher plasma sodium and significantly lower serum magnesium levels in patients with uncomplicated essential hypertension than in normal controls however serum potassium levels were not significantly altered Similar findings have been observed in patients with adrenal cortical hyperactivity Although this finding is suggestive the electrolyte pattern is not completely typical of that due to steroids since the latter patients are much more likely to have a lowered serum potassium than an elevated serum sodium In contrast Hollander observed that total body sodium (Na^{+} space) total body potassium (K^{+} space) and extracellular fluid volume ($S^{35}O_4$ space) were not altered in patients with essential and renal hypertension as compared to normal controls while in Cushing's syndrome potassium was decreased and sodium and extracellular fluid volume were normal or increased[2] Other evidence against steroid hypertension being the result of electrolyte effects is the observation that SC 8109 (Searle 19 nor analog of 3 (3 oxo 17 β hydroxy-4 androsten 17α yl) proprionic acid γ lactone) may induce sodium diuresis and potassium retention in primary aldosteronism without a fall in blood pressure[33] On the other hand SC 6584 (Searle 17 propyl 4 5 β dihydro-19 nortesterone) produces a lowering of blood pressure in metacorticoid perinephritic and adrenal regeneration hypertensive rats and increases sodium excretion[34] In addition patients with essential hypertension have been found to respond qualitatively the same to the Hickey Hare test as those with Cushing's syndrome[35]

Hypertension might also result from increased sensitivity of vascular smooth muscle to epinephrine and norepinephrine this might be induced by a direct steroidal effect on these tissues or by changes in electrolyte concentrations in these tissues[8] However recent data[36] indicate that reactivity of blood vessels to epinephrine and norepinephrine at least in experimental hypertension when aortic strips are tested in *in vitro* assays is not greater than normal and may even be diminished

A third way in which the adrenals may be directly involved in the pathogenesis of hypertension is that of an intermediary and essential link in the development of renal hypertension That there is more than a "permissive" role is suggested clinically by the fact that 60 per cent of patients with severe hypertension are significantly benefited by adrenalectomy plus limited sympathectomy even though receiving steroid replacement therapy[37] and by the fact that certain hypertensive patients who develop Addison's disease become hypotensive and although adequate replacement therapy is given (which should be sufficient steroids for a permissive effect) blood pressure is maintained at normotensive levels[38] This is further supported by the fact that the adrenal cortex is necessary for the development of renoprival hypertension and that adrenalectomy in the nephrectomized partner of parabiotic rats abolishes hypertension in the nephrectomized rat but is not necessary for maintenance of normal blood pressure[9] In experimental nephrogenic hypertension there is adrenal hypertrophy[8] and the width of the zona glomerulosa is increased by renin[40 41] On the other hand Fregly[4] was able to produce hypertension in adrenalectomized rats with latex encapsulation

of the kidneys and it is possible to maintain renal hypertension in adrenalectomized animals by administration of exogenous steroids

A fourth possibility is that in essential hypertension secretion of adrenal hormones is normal and that steroids have a permissive action rather than a direct effect That is to say that the presence of such hormones is necessary for the biochemical or other reactions responsible for the development of hypertension but that they do not exert any hypertensive effect in themselves [5, 40]

Finally it is possible that some patients with hypertension have an imbalance in steroid secretion leading to a disproportion in the amount of one steroid as related to another rather than hypersecretion of a given steroid as is present in Cushing's syndrome Such a disproportion could be present if the secretion of one steroid were in the low normal range and another in the high normal range yet in this situation secretion of individual steroids when considered alone would be normal Some evidence for this as a possible mechanism was the finding of a disproportionate secretion of corticosterone and hydrocortisone when adrenal glands from hypertensive patients were perfused *in vitro* [1] Excessive amounts of 11 dehydrocortisol and desoxycorticosterone with undetectable amounts of hydrocortisone have been found in urine extracts from one patient with congenital adrenal hyperplasia and severe hypertension [3] Corcoran noted that when renal hypertensive dogs were adrenalectomized and given "adequate" replacement therapy with specific hormones blood pressure was not fully restored to the previous hypertensive level whereas when adrenal cortical extract was given the pressure was restored Since it is likely that adrenal cortical extract may contain less hydrocortisone in relation to mineralocorticoids than is normally secreted steroidal imbalance could be a possible explanation in this situation Hypertension occurs in rats during the regeneration phase following adrenal enucleation [43] Here again it seems that there could well be disproportionate steroid secretion leading to hypertension

Thorn *et al* [39] reported that progression of vascular disease ceased in hypertensive patients who became Addisonian In these patients desoxycorticosterone increased blood pressure to prior levels and vascular disease progressed However when cortisone and desoxycorticosterone were combined patients could be maintained at normotensive levels This evidence suggests that while hydrocortisone may be hypertensive in itself when given in large doses physiologic amounts may counteract the hypertensive effects of salt retaining hormones In acute experiments in normal controls infusion of small amounts of cortisone has been shown to cause sodium excretion whereas larger amounts cause sodium retention [44] In addition to hydrocortisone other steroids may be secreted which have antagonistic effects to salt retaining hormones

Progesterone has natriuretic effects in normal subjects [45] but in Addisonian patients treated with cortisone alone no natriuresis occurs however if aldosterone is given to the same patient concurrently with cortisone progesterone then has sodium-excreting effects suggesting that this compound blocks aldosterone at the renal tubular level It could be postulated then that a chronic deficiency of such a substance might lead to excessive salt retention and hypertension although aldosterone secretion is normal In this regard it is of interest that 74 per cent of Schroeder's patients with the

"endocrine hypertensive syndrome" had menstrual disturbances and all patients had some abnormality of the reproductive system[6]

CONCLUSIONS

It is clear that in some well defined syndromes certain steroids from either endogenous or exogenous sources result in hypertension Such patients if untreated may develop all of the cardiovascular renal complications of so called essential hypertension *In these patients hypertension is* usually cured if therapy is instituted before severe vascular complications and resulting initiation of other hypertensive mechanisms ensue This group includes patients with Cushing's syndrome congenital adrenal hyperplasia primary aldosteronism and patients receiving large doses of certain steroids

In a second ill defined group of patients characterized by hypertension obesity menstrual disturbances and with a tendency to hirsutism edema acne and impaired carbohydrate tolerance but in whom a definite diagnosis of adrenal hyperfunction cannot be made using existing criteria there is a *strong suggestion that some hormonal imbalance is the responsible etiologic factor* This is in part borne out by the not infrequent finding of pathologic lesions in the adrenal cortices of such patients In Schroeder's clinic 20 per cent of all hypertensive women could be placed in this category

In hypertension known to be primarily due to renal disease the adrenal glands may play an important secondary role Although there is little clinical evidence to support this hypothesis experimental work indicates that under certain circumstances adrenal cortical function must be present for the development of renal hypertension However this role may be permissive *rather than a direct participating one*

Finally there is a large group of patients with "essential" hypertension In these patients hypertension can often be abolished by adrenalectomy and some studies have shown increased urinary excretion of cortical steroids notably those of Genest *et al* who demonstrated a moderate increase in aldosterone excretion In addition adrenal weight can be correlated with the level of diastolic pressure On the other hand steroid excretion has been normal in many hypertensives and it is possible that all of the above observations could be explained on the basis of a permissive role of adrenal *hormones and the stress of prolonged hypertension* To be explained are certain electrolyte abnormalities suggestive in some instances of a steroid effect Certain new *synthetic steroids* as well as certain normally secreted adrenal steroids have an antagonistic action to salt retaining corticoids and it may well be that an imbalance between these two groups of steroids is the etiologic factor in a portion of the patients now classified as having "essential hypertension

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Discussion

William A Sodeman *Moderator*

A C Corcoran	George Meneely
J Richard Crout	Lewis Mills
Lewis Dahl	Leo Sapirstein
Harriet Dustan	Henry Schroeder
Robert Gaunt	Sheldon Sommers
Arthur Grollman	Mordochai Toor
Phyllis Hartroft	George Wakerlin
G M C Masson	Bertram Winer
Milton Mendlowitz	

Dr Sodeman Dr Corcoran when you use the term permissive action" what do you mean?

Dr Corcoran I really don t use the term very much It was introduced by Dr Ingle as an explanation for some of the actions of the adrenal steroids in various nonadrenal states An action might be permissive in the sense that activity is exerted by one organ but only in the presence of the normal activity of another The latter permits a thing to happen but doesn t necessarily induce this action and it s the secondary mechanism which sustains This may be the case in established hypertensive vascular disease in that the mechanisms which sustain it may not have been primary causative factors

Dr Schroeder It seems to me that in patients with essential hypertension we must be dealing with several different disease entities and that our diagnostic tools are insufficient to pick out the differences in these diseases just as measuring blood sugar does not tell you what kind of diabetes a patient has As for the endocrine hypertension syndrome we called it that because at that point there was no aldosterone available it had just been discovered We didn t want to call it adrenal hypertension at that time which is what it probably is I think this is a clear group of cases which one can pick out on inspection of the patients These patients also have a low sweat sodium *I think that they probably are different from the other hypertensives who* have a normal sweat sodium and that we can probably take them away from the essential hypertension group

Dr Grollman I am skeptical of the existence of endocrine hypertension as an entity Since the adrenal cortex is associated with so many actions of the body there has been the tendency to attribute every deviation from the normal to some adrenal abnormality Long before the term permissive" began to be used the adrenal was held responsible for hypertension as well as other disorders now known not to be due to abnormalities in adrenocortical function Since desoxycorticosterone and the other mineralocorticoids increase the volume of the extracellular fluid we might anticipate that these hormones plus added salt in the diet combined with unilateral nephrectomy together should elevate the blood pressure If this elevation be maintained for a long time as in Cushing s disease obvious vascular lesions of the kidney

appear and we have a form of hypertension which is renal in origin So why *complicate matters if we can explain them on a relatively simple basis?*

DR GAUNT Would you make any distinctions between hypertension induced by the different corticosteroids such as DOCA and prednisone particularly *in regard to the effects on salt retention?*

DR GROLLMAN There is one distinction you have to make namely the distinction between the temporary rise in blood pressure which follows the use of the corticosteroids or large doses of salt and which disappears when you stop these medications and the permanent hypertension induced by prolonged steroid administration (which may occur spontaneously in Cushing s disease) which may induce demonstrable lesions in the blood vessel of the kidney Such chronic hypertension is different from the temporary elevation in blood pressure resulting from changes in blood volume and expansion of the extracellular fluid volume

DR SCHROEDER I agree with Dr Grollman that it is awfully nice to have different methods of producing the same end result However rather than having a unitary hypothesis for something as complicated as hypertension I believe that there are many different mechanisms by which blood pressure can be ordered out of normal range I think our animal experiments should *teach us clinicians that there are several ways in which hypertension can* be produced

DR MILLS I think that adrenal cortical activation may result in hypertension due to a number of etiological factors I think it is of great interest that one can simply walk around the wards and pick out these patients of the type described by Dr Schroeder and can just simply by looking at them know that they have hypertension and perhaps diabetes and so on This suggests that these patients are different Perhaps it is not primarily adrenal Perhaps it is pituitary or cortical or some other mechanism but there must be something different in these patients to produce this very characteristic physical appearance

DR DUSTAN *I don t think there is any such thing as essential hypertension!* I think that the term is merely an indication of how little we know about clinical hypertension Dr Schroeder is quite right that we should look and look carefully for all the types of the clinical counterparts of experimental hypertension This is where those of us interested in the clinical aspects of hypertension have our greatest future which is to gradually break away from the large group of so called essential hypertensions those people whose hypertension can be found to have a cause

DR HARTROFT I can t *help wondering if there isn t some way in experi*mental animals of tying in the DOCA type of hypertension with renal hypertension

DR. WAKERLIN *There is* certainly some interrelation between DOCA hypertension and renal hypertension Evidence has been produced in the past that DOCA hypertension particularly meticorticoid hypertension involves

renal lesions which suggests that there is a renal factor coming into the picture I think there are many interrelations between the adrenal cortex and the kidney at least in the rat as was indicated earlier in the day Some years ago one of our research group found that giving large doses of DOCA to dogs resulted in a loss of the normal renin concentration in the kidney With regard to this question of whether essential hypertension is a single disease entity or whether it is a generic classification I think that the majority opinion is to the effect that it probably is a generic classification and that we will separate out certain species of hypertension when we learn pathogenesis better than we know it now but it is still possible that Dr Grollman might be right.

Dr Masson In 1951 we injected DOCA into rats and found that there was an increase in the glomerulosa of the adrenals Since that zone has been shown to be the site of formation of so called mineralocorticoids one of which is desoxycorticosterone we postulated that in renal hypertension at least in its acute stage there is secretion of renin which produces hypertrophy and hyperfunction of the adrenal cortex Desoxycorticosterone in turn affects the sodium or salt and water metabolism and produces hypertension which in turn affects the kidney and so you actually have a vicious circle This evidence was quite indirect in some respects

Dr Sapirstein Dr Grollman notes that the adrenal effects of hypertension are correlated with an increase in the volume of the extracellular fluid and suggests the possibility that it may be this increase in extracellular fluid volume which produces the hypertension I would like to ask him how he thinks this comes about It isn t clear to me why an increase in extracellular fluid volume should cause an increase in arterial blood pressure

Dr Grollman It is a fact that expansion of the extracellular fluid elevates the level of the blood pressure I prefer not to speak of hypertension unless it is a permanent condition The condition induced temporarily by injecting fluid into the blood stream at a very rapid rate or by giving DOCA and sodium chloride together which also expands the extracellular fluid volume is accompanied by an increase in blood pressure This is a temporary condition Only after vascular changes occur in the kidney is the condition permanent

Dr Masson We experimented with two groups of rats whose adrenals were enucleated and who were given 1 per cent saline On the 20th day of this experiment one group was placed on water instead of saline and immediately their blood pressure went down When saline was given again the blood pressure went up In the other group in which the opposite was done the results were exactly the reverse This I think is a little disturbing to think of as sensitization resulting from initial hyperfunction of the adrenals It is difficult to understand why you would get sensitization of the animals after such a long time and why if you remove the salt the blood pressure goes down

Dr. Meneely I would like to comment on this question of salt and blood volume and its relationship to hypertension I must say that I agree with

Dr Sapirstein I can t see for example why you should not get hypertension when you have an increased extracellular volume in say congestive heart failure and nephrosis Surely if it were just due to retention of salt you should get an elevated blood pressure It is not as simple as that It seems to me that there are two actions of the corticoids One is the action involving the retention of sodium It is possible that the retention of sodium is more important in the smaller blood vessels than in tissues as a whole The other is a question of vascular reactivity which is mediated by the glucocorticoids I don t think we'll get anywhere in all this discussion of steroids unless we get at the basic mechanisms and learn how they work with relation to the blood pressure

Dr Sapirstein In line with this same point although a great deal of very careful work has gone into the study of hemodynamics such as in dogs made hypertensive by interference with the renal circulation there is a lack of measurements of the cardiac output in hypertension due to the administration of adrenal steroids The hypertension which is seen in various disturbances such as in adrenal regeneration may not be a true hypertension due to increased peripheral resistance but may represent only an increase in the cardiac output The hemodynamics of adrenal regeneration hypertension differs from that of renal hypertension In the former there is an increase in extracellular fluid volume which is not seen in the latter

Dr Dahl There are two terms that have been recurrent in this present discussion about which there should be some question namely sodium retention and hypertension and "increased extracellular fluid volume and hypertension I am not aware of any data which would suggest that there is more sodium retention in people with existing hypertension than in people without There is a very considerable body of evidence that they do not have more sodium I am not aware of any evidence which suggests that people with existing hypertension have more extracellular fluid Of course you can say that during the inception of the disease these two phenomena were present and then it became a self perpetuating disease

Dr Wakerlin Those who study the various forms of experimental hypertension are more and more impressed with the fact that there are many inter relations between different forms of experimental hypertension You can produce experimental hypertension by changes in nervous system function by changes in adrenal function particularly adrenocortical function and by changes in kidney function but if you start with one eventually as the animals continue over a period of months or years you get changes in the other two areas also Over a long period of time the different types tend to resemble each other somewhat although they still differ in etiology

Dr Sodeman Then in essence you agree with Dr Grollman

Dr Dustan Dr Mendlowitz I would like to ask you what effect hypervolemia and oligemia have on the responsiveness of the arterioles and the digital vascular beds to norepinephrine? You skirted this problem very nicely in the book you wrote although you did make some mention that these things possibly play a role It is very obvious that if you have a high plasma volume you probably have an increased cardiac output You have

a lot of changes which would not occur if you had normovolemia or what ever you wish to call it And are these changes only in the central circulation as it were or are there changes reflected in responsiveness in the peripheral vascular bed?

DR MENDLOWITZ I skirted that subject for a very good reason At that time we had not done any work on vascular reactivity I can only say that there is no question that when you change blood volume by a drug like Diuril and presumably reduce the cardiac output this is reflected in the periphery and that after the inhibition of sympathetic nerve discharge you are able to demonstrate less effect on blood flow than you d expect in normal subjects The results parallel what is found in the systemic circulation as a whole

We would like to be able to tie the sodium problem in with the question of vascular reactivity Unfortunately it does not tie in at least in the experiments that we have done so far We have given Diuril to patients with hypertension but have not been able to demonstrate any change in vascular reactivity by the methods that we used

DR DUSTAN What about hypervolemia?

DR MENDLOWITZ We haven t done it but my guess is that there would be no change from the normal

DR SCHROEDER I would like to ask Dr Dahl a question Several years ago it was claimed that people who were put on a low salt diet or rice diet got a decreased response to norepinephrine given intravenously but Dr Dahl was unable to confirm those observations I wonder if you have any explanation for that because if that were so we have a very nice theory at least a basis for how DOCA and salt work And certainly the counterpart of DOCA and salt adrenalectomy does show decreased responsiveness to sympathomimetic agents It s been known I suppose for forty years

DR DAHL Actually I was very excited when I saw that work because a great deal of my own work has been attempting to explain the mechanism of a fall in blood pressure following sodium restriction and I was fully prepared to confirm these data but in the seven patients that we studied at Brookhaven where we have facilities for studying them over many months I was not able to confirm it I don t have any explanation and it is a disappointment to me not to be able to because as you say it was a very elegant explanation

DR SODEMAN Dr Sommers do you have anything you would like to say about the relationship of these problems in the adrenals as we see them and renal hypertension as you discussed it previously?

DR SOMMERS In 80 per cent of human patients with essential hypertension adrenalectomy reveals the zona glomerulosa to be significantly smaller than in the control material This would indicate an abundance or excess of sodium in the extracellular fluid This is as far as one could go pathologically There is no doubt that some of Dr Schroeder s fat ladies are in this

group which is also of interest in endocrinology and in gynecology because they have a tendency to diabetes to endometrial hyperplasia and to cancer and they have definite changes up as high as the anterior pituitary and maybe in the hypothalamus Dr Ralph James of Iowa, and I studied the kidneys from rats treated with DOCA and saline There was a sticky sub stance layered along the inside of the glomerular and arterial capillaries which looked like fibrin but which you couldn t see in routine stain, but red cells were stuck together and we thought this was of importance in this particular hypertension It is a localized stickiness of the vessel walls This is probably not helpful to you but that s the pathology of these situations as I have seen them

DR WAKERLIN I would like to ask Dr Gaunt if he thinks that even though there is a decreased secretion of adrenal corticosteroids in adrenal regenera tion hypertension it is still possible to produce hypertension on the basis of an imbalance namely a little excess of mineralocorticoids over glucocor ticoids even though these are actually decreased on an absolute basis Might this imbalance be responsible for the hypertension?

DR GAUNT That is a very attractive hypothesis and one that I think peo ple like Dr Masson have looked for The only trouble is so far as I am aware that there is simply no evidence for it I don t mean it does not exist

DR SCHROEDER I don t see why steroid hypertension is so complicated If you happen to encounter an adrenal tumor or abnormal hypersecreting tissue it could be aldosterone or glucocorticoids and this eventually gets into the mechanism of hypertension If you happen to get blocked carotid arteries so that you don t get enough blood to your brain you get hyper tension and it again goes into this same blood pressure sustaining mechanism If you happen to get a plug in your right renal artery it obstructs a good deal of the flow and you get hypertension We call that renal hypertension but again it goes into the same vicious circle Why can t we accept steroid hypertension and call it such just as we accept renal hypertension and call it such and accept many neurogenic hypertensions and call them such? I don t see that it s quite as complicated as we are trying to make it What is complicated are the initial pathways that go into this thing and just how it happens but the maintenance of the thing seems to be quite clear cut

DR GAUNT I expect that we are now considering this problem at a stage where good hard quantitative measurements of a few of these variables might add a great deal more life than all kinds of theoretical discussions If we knew precisely that in a given type of hypertension there was a hypersecre tion of one or another of a group of corticoids or knew that in another type there would be diminished secretion we would have really solid quantitative evidence along those lines I think a lot of things that now seem obscure might become suddenly clear

DR MASSON When you obtain a certain reaction in an animal that does not mean necessarily that you are going to get exactly the same result in another species We talk about sensitization as a result of hyperfunction but we don t believe too much in that because in the rat you cannot get

hypersensitization following adrenalectomy and injecting steroids You could get that in humans that s true but not in the rat In the rat it is very easy to produce hypertension with desoxycorticosterone In a dog I don t think that there is any evidence that you could produce real hypertension that is the malignant type of hypertension that you have in the rat But you ve got to be very careful when jumping from one species to another and when applying an animal experiment to humans

DR GROLLMAN So called adrenal regeneration hypertension may be explained satisfactorily on the basis of potassium depletion It must be emphasized that in adrenal regeneration hypertension several factors are operative The subject must be a rat the dog fails to develop hypertension under the same conditions One kidney must be removed and the animal must be fed an excess of salt Young animals rats or dogs if placed on a potassium free diet at the time of weaning also develop hypertension later when they grow up The administration of substitutive adrenocortical therapy following enucleation of the adrenal prevents the development of hypertension

DR MENDLOWITZ I agree with Dr Grollman that we should not unnecessarily complicate matters Maybe our clinical experiences in New York are somewhat different from those of Dr Schroeder We have fat ladies with and without moustaches and with and without hypertension admitted to our wards for study Not infrequently despite a thorough endocrine workup we come up with the conclusion that they are simply fat ladies with moustaches or that they have essential hypertension Despite the desire of all of us to pick out the cases about which we can do something especially cases of aldosteronism pheochromocytoma etc most patients that we see on the ward with severe hypertension are still labeled essential hypertension"

DR SOMMERS From the retrospective point of view of pathology the vast majority of the cases of Dr Smithwick s material that I have seen would be considered essential hypertension but there is this minority with the adrenal adenoma Not all of these patients are Dr Schroeder s fat ladies some are even men and in this group we just don t have a very good diagnostic test I think there is an opportunity for future research because only from 5 to 25 per cent of these adenomas produce aldosterone They give all indications of a functioning tumor the steroid of which is as yet unidentified and it may be important in cancer just as it is in hypertension because this group includes some that have cancer

The Effect of Salt and Other Electrolytes in Hypertension

GEORGE R MENEELY

Vanderbilt University School of Medicine

What am I Life? A thing of watery salt
Held in cohesion by unresting cells
Which work they know not why which never halt
Myself unwitting where their master dwells?
JOHN MASEFIELD SONNETS 14

It is perhaps of interest that a collection of papers by distinguished authorities assembled to discuss hypertension in September of 1950[1] did not contain any title such as "Electrolytes in Hypertension although on reading the text it is manifest that electrolytes were very much a matter of concern to many of these authors Braun Menendez summarized All the factors which favor the retention of sodium in the organism whether due to an increased ingestion or to a decreased excretion facilitate the obtainment of hypertension (p 146) He cited most of his and other early experimental work on salt in hypertension which confirmed him in this conviction including the evidence that excess salt alone was nephro toxic and hypertensigenic (Selye Sapirstein Lenel and others) In that same symposium Chapman s paper (p 504) on the rice fruit diet of Kempner was most closely related to electrolytes as such in hypertension but the comments of McQuarrie following Chapman s paper are of special interest to us So far as we know his experiments there cited which were originally reported in 1936 contain the first clear cut evidence of the antagonistic role of potassium to the hypertensive effect of an excessive intake of sodium

It is not easy to trace the thread of truth through the history of salt and for potassium the past is even more uncertain Chapman s historical review in the article above mentioned[1] might be annotated to include the work of Schmidt[3] long incorrectly cited as the first clinical work on blood sodium Gamble in his 1952 Robert J Terry Lecture[4] described (and reproduced in its entirety) the 1831 report of W B O Shaughnessy[5] Scientific knowledge of potassium and sodium cannot precede the first decade of the nineteenth century because it was not until that decade that these elements were identified both in 1807 by Davy Davy also named chlorine in 1810 although it had been isolated in 1774 by Scheele who called the greenish yellow gas "dephlogisticated marine acid" and thought it contained oxygen The history of sodium chloride cultural and physiophylic has been reviewed by others and by us[6 7] in recent years The history of potassium is much more difficult to trace and is hazier in all departments

It may be that man s knowledge of potassium is really older than his knowledge of sodium The earliest known medical document a catalog of prescriptions on a baked clay tablet 4000 years old includes potassium

nitrate as an ingredient of a number of medications[16] All the existing evidence leads us to believe that knowledge of potash antedated recorded history most probably by many centuries It is speculative whether solar evaporation of sea or saline spring salt or the mining of native rock salt antedated or followed extraction of potassium salts from wood or plant ash or from naturally occurring efflorescences It is clear however that in some regions potash extracted from plant ashes was used as a condiment as was common salt elsewhere

Many have questioned why humans add salt to their food and the answer is not yet There is some evidence that salt is habit forming in the clinical sense[5] Von Bunge if not the originator of the notion certainly supported the thesis that an herbivorous diet because of its high potassium content (not any deficit of sodium chloride as such) impelled the eating of extra salt Witness he pointed out the treks of the herbivores to salt licks while the carnivores trekked not Louis Lapicque in a charming ethnographic inquiry published in 1896 gently pricked the subsequent cultural anthropological bubble[17] He showed herbivorous humans busy in lixiviation of plant ashes to prepare *their* salt which was the chloride of potassium not sodium—all this sometimes less than fifty kilometers from the sea The care with which Lapicque's savages selected the particular plants was not as others had thought because these plants had relatively high sodium content but quite simply because their lixivium gave the tastier chloride (with a little sulfate admixed) not the nauseating carbonate of potassium (salt of wormwood) more usually present in plant ash It is of interest that some of his approximations were based on a crude photometric technique

The ancient literature of salt meaning sodium chloride is fascinating and much of it really is about sodium chloride (although some salt licks contain none) but confusion holds sway when one turns to potassium Nitre is an ancient word (Latin *nitrum* whence natrium and then Na and Greek νιτρον and something else before that perhaps) but it means two things *natron* which is the native sesquicarbonate of soda but also potassium nitrate saltpetre Saltpetre means three things potassium nitrate sodium nitrate (Chile S) and a calcium salt (Wall S) Kali means alkali and also *Salsola soda* which is Barilla a maritime plant from which an impure *alkali* may be produced which is used in making soda, soap and glass Alkali is an adaptation of the Old French *alcali* which is an adaptation ultimately from the Arabic *al qaliy* formed on *qalay* to roast in a pan Thus originally *kali* which came out of the Arabic went back into late decadent Latin as *kalium* to stand as the name for potassium (and its symbol K) while the roast in the pan" Arabic origin certainly refers to the lixiviation of the calcined ashes of marine plants resulting largely in soda ash Here indeed is confusion confounded! Lapicque clearly saw the whole matter long ago concluding that it was the condiment and not the nutrient quality that impelled men to make and use salt whether the sodium or the potassium "It seems to me that there remains only one possible explanation of the usage of salt that is to consider it as a condiment and not as an aliment that is to say as an agreeable substance at the same time useful by its action on the senses not at all as a substance necessary to the incessant reconstruction of the organic edifice" Which of these were *a la mode* in any particular locale he supposed was the result of pre alchemical dabbling which led to primitive manufacturing processes The crystalline products depended

upon the available raw materials and the relative solubilities of the salts in the process ash (= lix, whence lye)

It may be fascinating and even intellectually stimulating to probe into the past in this vein but it is clearly of no particular service to pursue it in detail When all is done, the question "Why does man eat salt?" remains unanswered It is not even clear when he began to eat it Perhaps we never shall know

We need to know the answer to the question "Should man eat salt and if so how much is enough? The evidence from human studies is fragmentary In a later section of this symposium the information about humans will be touched on [18] but a more coherent picture can be adduced from life long studies in lower animals

Isaac Starr has pointed out that it is difficult to conduct an impeccable clinical experiment In the case of life long human experiments the technical and intellectual obstacles are overwhelming For this reason our "clinical studies are of rats not humans It is not really possible to conduct an impeccable experiment in lower animals either but the number of uncontrolled variables in life long studies can be reduced immeasurably Our interest of course is in the human and every caution must be employed in transferring implications from rat to man Still manufacturers of pharmaceutical products have learned to respect this rodent they have little confidence in a drug found effective in the dog but if it manifests an effect in the rat their experience indicates a fairly high level of correlation in the human

We have recently reviewed our entire experience with high sodium chloride feeding (with and without extra potassium chloride) based upon observations over the entire life span of 825 rats [19] This represents eight separate experiments From these data one can construct at least the ground plan of the long term effect of excess sodium chloride ingestion and something of the way in which extra potassium chloride favorably influences its noxious effects

The levels of sodium chloride fed are detailed in our earlier reports In retrospective analysis it became apparent that our numerous dietary sodium chloride levels fell into four fairly clearly defined categories low" "control "moderate" and "high salt feeding While in some parameters the data are a continuum in others there are "break points" or discontinuities Only one diet explored the low salt region Although of interest from the point of view of nutrition it is not especially relevant to our purpose here save to help define the lower limit of the control" region The basic ration with no extra sodium chloride contained 0 01 per cent sodium as NaCl This was compatible with growth but survival was poor (Fig 1) after the fifteenth month

Diets which contained from as little as 0 15 per cent sodium chloride to as much as 2 0 per cent sodium chloride all seemed to us to be in the control" region At 0 15 per cent growth was slightly less rapid than at the somewhat higher levels of salt but survival was in no way different nor were blood pressures or anatomic findings different From 2 8 per cent to 5 6 per cent sodium chloride in the diets represents "moderate elevation of dietary salt Diets containing 7 0 per cent and above were manifestly "high" levels of excess salt feeding

MONTHS ON DIET

0 2 4 6 8 10 12 14 16 18 20

% SURVIVAL

100 90 80 70 60 50 40 30 20 10

0.15% NaCl

0.01% NaCl

Fig 1 Survival of rats eating 0.01 per cent (low salt) and 0.15 per cent NaCl (control) (J Gerontol 12 186 1957)

RATS EATING VARIOUS LEVELS OF NaCl

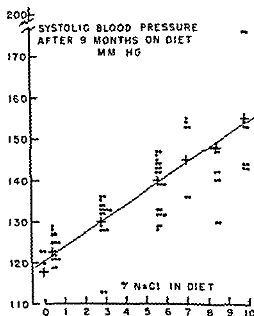


Fig 2 Relation of blood pressure to dietary NaCl (J Am Dietet A 33 386 1957)

On a calorie for calorie basis 2.8 per cent sodium chloride added to the purified basic animal ration is equivalent to about 14 gm per day of salt in a human dietary providing 2500 calories In the rats as will be seen 2.8 per cent is a frankly hypertensigenic level of salt intake

For our purposes today the most interesting observations made on these colonies was that of the effect of extra dietary sodium chloride on the blood pressure In Figure 2 may be seen the blood pressures after nine months on such diets The actual values observed in any one group of animals exhibit wide scatter within individual levels of sodium chloride feeding Figure 3 shows the statistical analysis of the same data (plus and minus one standard error of the mean) clearly illustrating that there is a simple linear relation

MEAN AND STANDARD ERROR OF THE MEAN FOR EACH OF THE SEVEN GROUPS

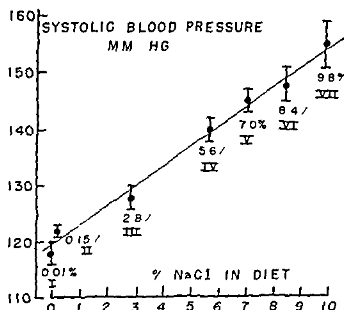


Fig 3 Mean blood pressures after 9 months on experimental regimen (Am J Med 25 716 1958)

ship between the blood pressure and dietary sodium chloride level It is of interest that those severely hypertensive in any one group at any one time were the same as those severely hypertensive at a later date while those whose levels of blood pressure were well below the means of a group continued to occupy these lower levels throughout their lives

Electrocardiographic studies were done on a large number of the animals at several times during the experiment and the incidence of electrocardiographic abnormalities was found to be directly proportional to the amount of salt in the diet (Fig 4) As an additional point of interest the specific abnormalities observed were closely similar to those of human hypertensive subjects namely a high incidence of T wave abnormality S T segment abnormality left axis deviation left ventricular strain pattern and prolonged duration of the QRS complex Arrhythmia and prolongation of the P R

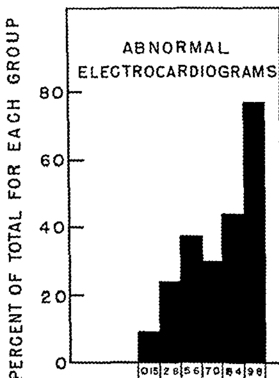


Fig. 4 Incidence of abnormal electrocardiograms in rats eating various levels of NaCl after 19 months (J Gerontol *12* 184 1957)

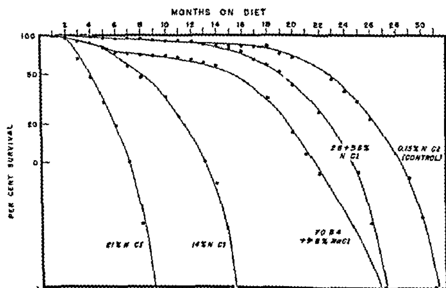


Fig. 5 Survival of rats eating 0.15 to 21.0 per cent NaCl (J Gerontol *12* 160 1957)

interval occurred only rarely It was also of interest that the incidence of electrocardiographic abnormality was clearly related to the severity of the hypertension

Studies of serum cholesterol revealed a tendency for increase with increasing dietary sodium but a considerably more interesting correlation is that of the cholesterol level in the blood and the blood pressure This proved to be highly significant ($r = 54 \pm 12$) but of further interest is the fact that no animals with normal blood pressure showed elevated cholesterol Various other abnormalities of lipid metabolism have been discussed in some detail in previous publications

Perhaps the most revealing observations of the entire study are the data pertaining to survival (Fig 5) Animals eating control levels of sodium chloride did not show a significantly different survival from those eating moderately increased sodium chloride (2 8 and 5 6 per cent) until after about the seventeenth month Thereafter highly significant differences in survival were clearly apparent for the group These rats exhibited a hypertension the character of which was essentially benign If ten days for a rat is equivalent to a year for man at an age equivalent to age fifty for man these rats began *to exhibit an accelerated mortality rate Progressively* higher levels of salt feeding produced progressively greater decreases in the survival rate

The anatomic findings are of considerable interest At high levels of high salt feeding when severe hypertension occurred the changes resembled closely those of human malignant hypertension At lower levels of high salt feeding when the blood pressure elevation was only moderate and when the course was essentially benign the anatomic findings by ordinary histopathologic techniques were not significantly different from those of controls Quantitative studies of organ weights however did reveal a progressive increase in heart weight proportional to the increase of sodium chloride in the diet and a progressive increase in kidney weight proportional to the increase of sodium chloride in the diet However when attention was directed to the adrenals *only at the highest level of salt feeding* was a significant increase in adrenal weight observed Dr Ernest Goodpasture observed an interesting point in those animals eating high levels of salt (9 8 per cent) namely that there was an invariable association of severe arteriolar disease in the testes when severe renal vascular lesions were found He suggested that this might serve as a method of study of the pathogenesis of the lesions because of the availability of the testes for biopsy

For reasons which we have discussed at length elsewhere we later explored the effect of additions of potassium chloride to diets high in sodium chloride The results of these observations at two levels of increased salt feeding one "moderate" and one "high are seen in Figures 6 and 7 The solid line represents the survival curve established by 53 rats eating control levels of sodium chloride in each case It may be seen that rats eating 5 6 per cent sodium chloride *without increased potassium chloride had a survival* considerably less than that of the controls On the other hand when 2 9 per cent potassium chloride was added to the 5 6 per cent sodium chloride we were embarrassed to discover that the survival of these animals was better than that of those eating our "control diet This certainly suggests that the control diets may be suboptimal in potassium At still higher levels of salt feeding namely 8 4 per cent the protective effect of potassium is again

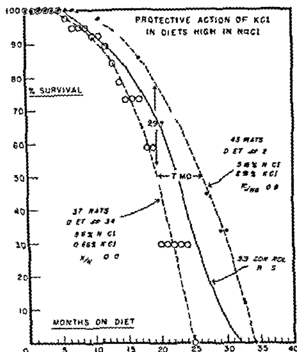


Fig 6 Survival of rats eating 5 6 per cent NaCl with and without added KCl (Ann Int Med 47 267 1957)

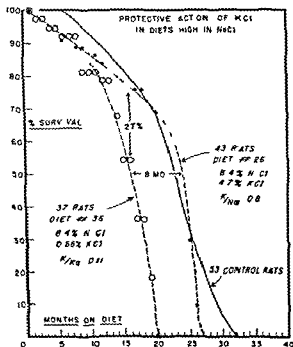


Fig 7 Survival of rats eating 8 4 per cent NaCl with and without added KCl (Ann Int. Med. 47 268 1957)

clearly manifest In each case at the time 50 per cent of the high salt eating unprotected rats were dead nearly 80 per cent of the potassium protected rats were alive and seven or eight months passed before the median duration of life was reached by the protected group of animals receiving extra potassium chloride Of even greater interest are the observations on the blood pressure in these two groups of animals as illustrated in Figure 8 and Figure 9 It may be seen from the first of these figures that the addition of 2 9 per cent potassium chloride to a diet containing 5 6 per cent sodium chloride does not alter the moderate hypertension of moderate increased salt eating in any significant way In contrast when extra potassium chloride is

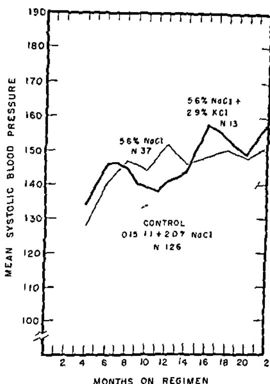


Fig 8 Blood pressure of rats eating 5 6 per cent NaCl with and without added KCl (Ann Int Med 47 269 1957)

added to 8 4 per cent sodium chloride diets the high hypertension characteristic of the unprotected high salt eating animals does not develop The blood pressure in effect is held at the intermediate level which is usually characteristic of the feeding of intermediate levels of increased salt Thus there are at least two sorts of hypertension in high salt eating rats

It is of great interest in this connection to note that the total body sodium of animals eating 8 4 per cent sodium chloride and above is greatly increased over that of control animals (Fig 10) while the total body sodium of animals eating 5 6 per cent sodium chloride or less is not increased over that of controls Further when extra potassium chloride is added to the "high" levels of salt feeding such as the 8 4 per cent sodium chloride diet the accumulation of excess total body sodium does not occur It is tempt

ing to link these two although one cannot claim concurrence as a basis for a causative relation Certainly there is a strong association

Perhaps these observations on the effect of potassium added to diets high in sodium chloride may give a clue to the puzzling picture in humans It is clearly evident from these studies that with regard to sodium intake and potassium chloride intake there are at least five quite different kinds of rats First there are those eating a "normal" intake of sodium and a "normal" intake of potassium who live a long life and never exhibit elevation of the blood pressure The second group are those who eat a moderate increase of dietary sodium chloride This group is characterized by diminished survival

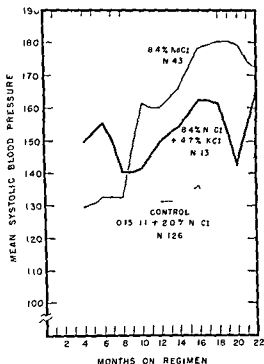


Fig 9 Blood pressure of rats eating 8 4 per cent NaCl with and without added KCl (Ann Int Med 47 270 1957)

and a moderate life long elevation of the blood pressure The third group are those animals who eat a moderate increase of sodium chloride but who also eat increased potassium chloride In these animals the blood pressure elevation is the same as in the second group of animals but the duration of life is greatly prolonged Survival is actually a little better than that of the control animals under the circumstances tested in our experiments The fourth group of rats are those eating high levels of excess sodium chloride These are characterized by high hypertension greatly shortened life span and increased total body sodium Finally the fifth group of animals are those eating high levels of excess salt but also eating extra potassium chloride The clinical picture in these animals is characterized by a moderate hypertension and their survival is prolonged to become equal to that of the control animals Further the increased total body sodium observed in the

fourth group of rats is not seen in this fifth group Thus the extra potassium chloride at moderate levels of salt feeding produces only prolongation of life without amelioration of the moderate increase of blood pressure characteristic of moderate excess salt eating On the other hand at high levels of excess salt eating the addition of potassium chloride not only produces a substantial prolongation of life but reduces the blood pressures observed to those of an intermediate level more characteristic of the moderate sodium chloride intake and concurrently it appears to prevent the accumulation of excessive total body sodium

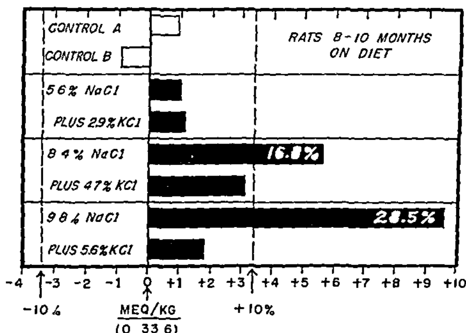


Fig 10 Exchangeable sodium determined by method of isotope dilution using radioactive sodium 24 (chemical sodium measured by flame photometry Coleman Instruments Inc., Model 21 flame photometer) (Ann Int Med 47 271 1957)

Perhaps the difficulties which have been encountered in attempting to reconcile the discordant observations on sodium chloride in human hypertension and on added potassium in human hypertension may be explained by the complexity of the over all picture It appears likely that a search would reveal at least five kinds of humans just as it has clearly shown five different kinds of rats with respect to the intake of sodium chloride and potassium chloride Some of the frankly clinical and therapeutic implications of these observations are discussed later in this symposium [18]

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Sodium as an Etiologic Factor in Hypertension

LEWIS K DAHL

Medical Department Brookhaven National Laboratory

In modern societies the addition of salt to food is so commonly practiced that it might come as a surprise to learn that there are whole groups and races which never add salt to food during its preservation cooking or eating Among those that do add salt there appear to be groups which ingest significantly more than others [1] Since there is evidence that salt is implicated in the hypertensive process wide variations of intake among individuals and groups suggested the possibility that high salt intake and essential hypertension might have a cause and effect relationship [2-8]

SALT REQUIREMENTS

Although classification of salt intakes as "high" or low is dependent largely upon the dietary intake of the observer it is possible to compare intake with requirement and thereby arrive at some relative evaluation With individuals given free choice there is no necessary relationship between optimal food requirements and actual food intakes as exemplified by the fat and caloric intake of many Americans Relative to salt estimates of daily need ranging from 5 to 15 gm of sodium chloride have been made [7] but Allen[9] has written that adults certainly required less than 2 gm per day During the past 10 years the author and associates have made a variety of metabolic studies[10-15] on ambulatory hospitalized patients with and without hypertension who have been maintained on diets which contained about 40 to 175 mg sodium (100 to 440 mg as NaCl) a day for months to years the longest study was on a woman who had a known sodium intake of 100 to 150 mg a day for almost 5 years [1] Except for those with very poor kidney function these subjects remained in salt balance without difficulty were active and had no symptoms signs laboratory findings or functional tests suggesting that salt restriction of this degree was inadvisable [7] From our studies we have found the normal "obligatory" (or minimal) daily sodium losses to be about as follows stool 10 to 125 mg skin (nonsweating) 25 mg urine 5 to 35 mg a total of 40 to 185 mg Estimates of other bodily losses indicate that these would not exceed an average of 15 mg for a final total of not more than 200 mg per day (0 5 gm as NaCl) If liters of sweat were being lost every day it probably would be unwise to assume that salt balance could be maintained indefinitely on such a regimen Nonetheless I[7] and others[1] have found no need to add salt to the low salt diets of working people in temperate climates during the summer months and in my experience salt intakes at this low level for years have been compatible with normal activities outside the hospital

It should be no surprise then to learn that many vigorous peoples and

tribes for untold generations did not add salt to their food but ate only that contained in natural food stuffs Among such groups—and there are many—three may be mentioned which differ greatly in climatic geographic and cultural conditions Eskimos Northwest American Indians and the Masai of Africa Estimates or analyses of the salt intake of these groups indicate maximal intakes of about 5 gm., although others are less than 1 gm Indeed except where the drinking water has a high salinity it is likely that without the addition of salt to food a salt intake in excess of 4 or 5 gm per day is impossible

SALT INTAKE AND APPETITE

Analyses of actual salt intakes in western society are rare The several available estimates[7, 1, 18] are in general agreement that average intakes approximate 10 gm per day This would indicate that whereas metabolic balance can be maintained easily on daily intakes of 0 5 gm NaCl adult members of our society ordinarily exceed this twentyfold

Is this difference between intake and need due to subtle physiologic requirements and inborn appetite for salt or is it a taste habit which can vary with eating customs in different societies? The long travels of some animals to salt licks are well known less well known is the fact that it is the herbivores not the carnivores and omnivores which do this[19] although among all these it is possible to induce salt appetites In man it is unlikely that salt appetite is inborn for both Stefansson[20] and Holmberg[1] reported that the northern Eskimos and the Sirionos of Bolivia with whom they were respectively associated disliked salt when it was first offered but grew to like it with use Among my patients both with and without hypertension there have been none with evidence of salt craving after drastic salt restriction for years Mention has been made already of the fact that it was possible for vigorous tribes to flourish for generations on low salt intakes The foregoing evidence suggests that salt appetite is not inherent but is acquired by virtue of local food habits and social customs much like those of tobacco and alcohol in our own society

RELATIONSHIP OF SALT INTAKE TO ESSENTIAL HYPERTENSION

The administration of various sterols[22] particularly desoxycorticosterone acetate[3, 4] plus simultaneous salt ingestion has been for years one of the standard methods of inducing hypertension in animals Simultaneous salt ingestion appears to be necessary for the hypertensive effect of most but apparently not all steroids tested thus far Salt feeding with restriction of fluid (hypertonic saline as the sole source of liquid intake) will produce hypertension in the chicken[6] and rat[7, 8] without the use of supplemental steroids Finally Meneely and his group have shown that chronic ingestion of excessive NaCl *alone* will produce a pathologic process in rats that mimics human hypertension[23] Thus it seems clear that whatever the relation to human disease salt ingestion can induce hypertension in some animals

Salt restriction has long been used as part of the therapeutic regimen for humans with established hypertension The evidence that limitation of sodium results in a significant decline in the blood pressure of some individuals with hypertension is now so unequivocal that further amplification of

this point is unwarranted Recently we studied a variation of this problem namely the response of obese hypertensives to weight loss as well as to salt restriction [8] It has been reported frequently that weight reduction is effective in lowering blood pressure but in our experience no significant decline in pressure occurred during reduction to or toward ideal weights unless salt intake was limited the original observations have now been extended and confirmed

In those hypertensive individuals who respond to salt restriction elevation of the blood pressure usually results when salt is added to the diet again [10 33] If to the logician a decrease in pressure with decrease in salt intake and an increase in pressure with increase in salt intake do not constitute proof of a causal relationship between salt ingestion and hypertension to the epidemiologist they have been highly suggestive leads for further investigation Excessive salt feeding has been tried for short periods in normotensive adults with negative or inconclusive effects on blood pressure I think this not surprising for if excess salt ingestion does play a primary role in the pathogenesis of essential hypertension the fact that the disease is uncommon before the fourth decade suggests that length of *time* over which salt is ingested is also important In a few children with diabetes mellitus however salt ingestion has been shown to elevate the blood pressure rapidly [34]

Among peoples that are on a life long low salt diet *essential* hypertension appears to be relatively uncommon Since there are numerous causes of high blood pressure some hypertension will be seen among such groups but in no instance have I been able to find evidence suggesting that they have essential hypertension as commonly as or more than residents of the United States By contrast, there is considerable evidence that the disease is much less common and sometimes rare [7] Needless to say there are other differences in their lives as compared with those of the urban or even rural American nonetheless pursuant to the thesis in this paper the differences in salt intake appear to be prominent

In view of the foregoing experimental clinical and anthropological evidence which suggested that salt was involved in the hypertensive process it seemed reasonable to explore the possibility that among individuals who chronically ingested a high salt diet essential hypertension would be more common than among those on a low salt intake It was thought that some idea of salt intake in the American environment could be derived from use of salt at table although it was recognized that there are other sources of salt intake about which we would have no information [3 6] From 1953 to 1956 Dr Robert A Love of Brookhaven queried all employees who reported to him for their annual physical examination as to their customary salt habits during eating Individuals were placed in one of three categories (1) *low salt intake*—had never added salt to food at the table (2) *average salt intake* —added salt to food if after tasting it was insufficiently salty (3) *high salt intake*—routinely added salt to food without prior tasting There was no thought then nor is there now of suggesting this way of judging salt intake as a generally applicable one for it is obviously dependent upon local salt eating customs Recently for example I studied the same problem among the Japanese around Hiroshima where it was found that daily salt consumption as measured by 24 hour urinary sodium excretion was high but the salt was added to the foods and sauces before reaching the table Therefore these Japanese would have been classified as having low salt intakes by the

method described above Basically it was used to test a hypothesis in order to determine whether further exploration of the thesis was advisable

The data on 1346 consecutive subjects are shown in Tables 1 to 3 Very briefly it was found that the incidence of hypertension in these three groups

*TABLE 1 UNCORRECTED DATA ON SALT INTAKE AND INCIDENCE OF HYPERTENSION IN HUMANS**

SODIUM CHLORIDE INTAKE	TOTAL SUBJECTS NO	% OF TOTAL	SUBJECTS WITH HYPERTENSION NO	% OF INTAKE GROUP
Low	135	10 0	1	0 7
Average	630	46 8	43	6 8
High	581	43.2	61	10 5
Total	1346	100 0	105	7 8

The distribution of subjects with hypertension was significantly different among the three groups as tested by the chi square distribution with $x^2 = 16\ 1$ and $p < 0\ 001$

TABLE 2 SODIUM INTAKE BY AGE AND SEX OF SUBJECTS

SODIUM CHLORIDE INTAKE	AGE, YR	MALES NO	% OF INTAKE GROUP	FEMALES NO	% OF INTAKE GROUP
Low	35 2 (± 9 2)	101	74 8	34	25 2
Average	34 7 (±10 3)	522	82 9	108	17 1
High	34 4 (±10 0)	501	86 2	80	13 8
Total	34 6 (±10 0)	1124	83 5	222	16 5

Sex distribution significantly different among the three groups ($p < 0\ 01$)

TABLE 3 CORRECTED INCIDENCE OF HYPERTENSION IN MALES ONLY

SODIUM CHLORIDE INTAKE	AGE YR	TOTAL SUBJECTS NO	% OF TOTAL	SUBJECTS WITH HYPERTENSION NO	% OF ALL WITH HYPER TENSION	% OF INTAKE GROUP
Low	36 8 (± 9 4)	101	9 0	1	1 0	1 0
Average	36 1 (±10 7)	522	46 4	38	39	7 3
High	35 7 (±10.2)	501	44 6	58	60	11 6
Total	36 0 (±10 4)	1124	100	97	100	8 6

For all three groups $x^2 = 14\ 3$ and $p < 0\ 001$ for low intake group $x^2 = 7\ 42$ and $p < 0\ 01$ for high intake group $x = 5\ 54$ and $p < 0\ 02$

was significantly different from random distribution ($p < 001$) those on the low salt intake had less hypertension ($p < 01$) while those on the high salt intake had more ($p < 02$) hypertension than would have been predicted by chance[6] Obesity further increased the probability of hypertension among people on a high salt diet it was suggested that the obese person in eating more food ate more salt simultaneously and that it was this increased salt

intake rather than the obesity which accounted for the increased incidence of hypertension in overweight individuals. The study on obese hypertensives alluded to earlier[8] in which weight loss ordinarily did not result in a fall in blood pressure without salt restriction is in agreement with this postulate. In another study, as an index of salt intake the urinary sodium excretion of 28 ambulatory men with and without hypertension was measured for periods of 6 to 38 days (median 7 days). It was found that the men with hypertension ingested significantly more ($p < .01$) salt than the nonhypertensives. However, it was clear that even among the men without hypertension none was eating salt at the low levels found among groups in which essential hypertension is uncommon. If salt intake is important in hypertension one might predict that some of these relatively young men (average age 36 9 yrs) will become hypertensives in later years. The length of time over which salt is ingested must be an important factor in humans just as it is in experimental animals.

The cumulative evidence seemed sufficient to submit the hypothesis that *excessive salt (i e sodium) in the diet was a crucial etiologic factor* in the development of essential hypertension.[6] Allen in 1925[9] and Meneely in 1954[19] suggested a similar relationship.

It was of interest to investigate whether there might be entire groups or races which habitually consumed a high salt diet and this now seems to be true. It has been known for some years that the West Indian Negroes have a much higher incidence of hypertension than either whites or Panamanian Indians[4, 36, 37] and I have summarized the evidence that these persons have a high salt diet from early childhood.[7, 17] It is probable that by the time this article is published there will be ample quantitative data on this point, for I am informed that there are now several groups investigating salt intake in these Negroes.

Although it has been axiomatic that Orientals have little hypertension the Japanese are a striking exception.[1] The disease is common among them and cerebrovascular accidents are the leading cause of death in males from the ages of 50 to 80. Among one group of rural Japanese in which hypertension is very prevalent[1]—in Akita Prefecture studied by Prof T Fukuda of Chiba University—an average salt intake (based on 24 hour urinary chloride excretion) of 26 3 gm was found. In some 1200 Japanese living in a village near Hiroshima I recently found the incidence of hypertension to be greater than in the United States (paper in preparation); interestingly, measurements of 24 hour urinary sodium excretion indicated that the average salt intake was about 14 gm per day among the males, which may be compared with the average of 10 gm found in the Brookhaven male population. As nearly as the data appear comparable the relative incidence of hypertension among the males aged 20 to 60 at Brookhaven, Hiroshima and Akita appeared to increase with increasing levels of salt intake. If such a relationship exists it would be in agreement with the animal studies of Meneely's group.[4]

No doubt there are factors—dietary, hormonal, emotional, hereditary—which will influence the effects of various levels of salt ingestion. In an unrelated disease, namely rheumatic fever, there are a number of factors including heredity which predispose to development of the disease.[39] Yet without beta hemolytic streptococci infections[39] the predisposing factors above will not result in rheumatic fever. We believe that salt plays a similar primary role in essential hypertension.

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Studies of the Content and Distribution of Sodium, Potassium and Water in Human Hypertension

BERTRAM M WINER

Harvard Medical School and Beth Israel Hospital Boston

Abnormalities in sodium metabolism have been established in human and experimental hypertension but their primacy in the pathogenesis of essential hypertension has been in doubt The present studies were executed first to provide basic data concerning body water sodium and potassium in untreated essential hypertension and secondly to correlate the effects of chlorothiazide and reserpine on salt and water with their effects on blood pressure The effect on the blood pressure of added sodium or potassium during the administration of chlorothiazide was also observed

In the first study that of untreated patients with essential hypertension

24 hour exchangeable sodium and potassium extracellular fluid total body water and plasma volume were determined in 28 patients with essential hypertension and in 24 control subjects Malignant hypertension congestive failure edema of any cause and renal insufficiency were excluded

Data from males and females were analyzed separately because of the known sex differences in body fat content Total body water was significantly lower in the hypertensive than in the control groups Females had significantly lower values than males These findings are consistent with increased fat content in the hypertensive and female groups Per unit of body weight exchangeable sodium exchangeable potassium extracellular fluid and plasma volume were clearly not increased in the hypertensive group Mean values in the males are shown in Table 1 Values in the females were slightly lower

TABLE 1 TWENTY FOUR HOUR EXCHANGEABLE SODIUM EXCHANGEABLE POTASSIUM EXTRACELLULAR FLUID AND PLASMA VOLUME IN UNTREATED MALES WITH ESSENTIAL HYPERTENSION

	HYPERTENSIVES	CONTROLS
Na (mEq /kg)	41 3	42 2
K (mEq /kg)	45 6	50 5
ECF (% wgt)	15 6	16 4
PV (cc /kg)	38 5	42 5

The relationships of exchangeable sodium and potassium extracellular fluid and plasma volume to total body water were also examined and compared between the groups Small differences not statistically significant were observed Serum sodium and potassium were equal in the two groups Thus beyond differences ascribable to differences in fat content no significant differences in the content or distribution of water sodium or potassium were uncovered by these methods in a comparison of normal subjects with patients with untreated essential hypertension

In the second study the effects of 75 to 1 5 gm of chlorothiazide daily for 6 to 8 weeks were studied in 19 patients with essential hypertension Twelve of the 19 patients had previously been treated with reserpine with or without Apresoline and these agents were continued Seven patients received chlorothiazide alone Dietary sodium was not restricted

TABLE 2 CHLOROTHIAZIDE RESPONSE IN 19 PATIENTS WITH ESSENTIAL HYPERTENSION

Serum K	—0 7 mEq /L
Body wgt	—1 1 kg
TBW	—0 8 L
ECF	—1 1 L*
Na_e	—113 mEq
K	—61 mEq
PV	—152 ml
* = p < 05	≈ p < 01

In the group as a whole (Table 2) mean serum sodium was unchanged although mean serum potassium fell from 4 1 to 3 4 a change of 0 7 mEq /L Body weight fell approximately 1 kg body water and extracellular fluid

TABLE 3 RESPONSE TO CHLOROTHIAZIDE OF TWO PATIENTS RECEIVING RESERPINE BEFORE AND DURING STUDY

1 W R		2 C J	
Change in mean BP	−3 mm Hg	Change in mean BP	−35 mm Hg
Change in Na	−562 mEq	Change in Na	−33 mEq
Change in PV	−560 ml	Change in PV	+83 ml
Change in K	+264 mEq	Change in K	−499 mEq

approximately 1 liter Exchangeable sodium fell 113 milliequivalents and exchangeable potassium 81 milliequivalents There was a decrease in plasma volume of 152 ml a fall of 6 per cent Thus for the group as a whole there was a mean loss of approximately 1 liter of extracellular fluid and some loss of intracellular potassium Mean blood pressure fell 20 mm a change of 15 per cent

The responses of patients treated with chlorothiazide alone were essentially similar to the responses observed in those who had also been on reserpine with or without Apresoline Patients on reserpine however did lose slightly larger amounts of exchangeable sodium

Individual patients showed striking differences in response to chlorothiazide In some the excretion of sodium was favored in others the excretion of potassium There was no clear correlation between such changes and blood pressure response

Data in Table 3 concern the response to chlorothiazide of two patients

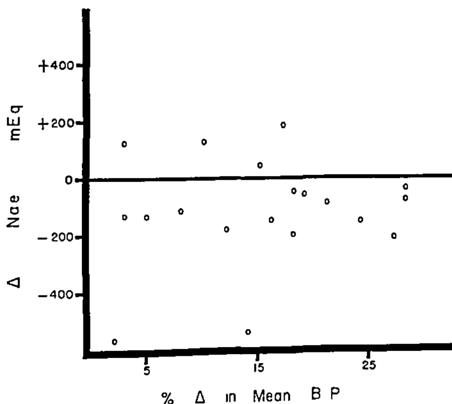


Fig 1

TABLE 4 EFFECT OF ADDED NaCl OR KCl DURING CHLOROTHIAZIDE

	CONTROL BP	RESPONSE
NaCl		
8 12 gm daily	147/86	148/84
KCl		
8 gm daily	149/83	154/88

each of whom had received reserpine before and throughout the study One patient had a large loss of sodium more than 500 milliequivalents a fall in plasma volume but no change in blood pressure The second patient had a large loss of potassium a small change in sodium or plasma volume and a marked fall in blood pressure

The lack of correlation between change in exchangeable sodium and per cent change in blood pressure is evident in Figure 1 A broad scatter of points is seen From a statistical point of view the correlation was poor The observed correlation coefficient r was — 12 Ninety five per cent con fidents limits were broad and included zero

A lack of correlation between change in exchangeable potassium and change in blood pressure and between change in plasma volume and change in blood pressure was also observed

Ten patients who had shown a fall in mean blood pressure of at least 10 per cent were given 8 to 12 gm of added sodium chloride a day for 2 to 12 weeks concurrent with the administration of chlorothiazide (Table 4) Control blood pressure refers to mean group blood pressure during chloro thiazide No significant change in blood pressure was observed There was also no significant change in blood pressure after the administration of 8 gm of potassium chloride daily During the administration of sodium chloride 24 hour urinary excretion of sodium was studied in several patients and was observed to rise approximately in proportion to the amount of added salt

In the third study the effects of reserpine were examined in 4 patients each of whom had been selected because of weight gain of 5 to 10 pounds in a period of weeks to months after administration of this agent (Table 5) Each patient gained more than 150 milliequivalents of sodium On an aver age dose of 1 0 mg a day given for months there was a mean increase in body weight of 3 2 kg a mean increase in exchangeable sodium of 311 milliequivalents and a rise in total body water of 2 liters Changes in exchangeable potassium and plasma volume were small Despite the increase in body sodium two of the patients had significant falls in blood pressure during the administration of reserpine Two did not

TABLE 5 EFFECTS OF RESERPINE IN FOUR PATIENTS EXPERIENCING WEIGHT GAIN

	MEAN BP (mm)	WGT (kg)	Na (mEq)	TBW (L)
B K	−31	+4 0	+300	+1 7
S D	−14	+2 6	+440	+4 1
M B	0	+4 5	+335	+0 4
F K	0	+3 1	+16[illegible]	+1 9
mean		+3 2	+311	+2 0

TABLE 6

	Na	K	BP
Aldosteronism	High	Low	High
Periodic paralysis	*High*	*Low*	*Normal*
Essential hypertension	Normal	Normal	High
Reserpine	Increased	Unchanged	Decreased or unchanged
Chlorothiazide	Decreased or unchanged	Decreased or unchanged	Decreased or unchanged

Other studies have shown that in both primary aldosteronism and in familial periodic paralysis exchangeable sodium has been high and exchangeable potassium low although the blood pressure is high in the one disease and normal in the other (Table 6) Furthermore certain abnormalities in sodium metabolism which have been established in hypertension namely increased salt appetite and increased salt excretion after salt load have been observed in hypertension of diverse etiologies (steroid renal and essential hypertension) In addition differences in sodium excretory capacity have been correlated with the height of the blood pressure and with changes in blood pressure Thus there is evidence to suggest that these abnormalities in salt metabolism may be secondary events

In summary although it is recognized that some change in intracellular electrolyte may not be discerned by present methods the studies reported today do not offer evidence of any abnormality in the content or distribution of sodium potassium or water in untreated patients with essential hypertension who do not have congestive failure or advanced renal disease Chlorothiazide usually lowered plasma volume extracellular fluid and to a small extent intracellular potassium However individual patients showed considerable variability and in some there was a predominant loss of one or the other cation The hypotensive response to chlorothiazide was poorly correlated with total sodium potassium or water loss and was not affected by the administration of large amounts of sodium or potassium Reserpine was observed in selected patients to increase body salt and water without necessarily interfering with the hypotensive response The increased extracellular fluid induced by reserpine was reversible by chlorothiazide

In conclusion these studies do not lend support to the thesis that an increase in body sodium is a primary pathogenetic factor in essential hypertension Indeed these studies suggest that moderate changes in body sodium may not influence the blood pressure strongly The precise mechanism of action of chlorothiazide as an antihypertensive agent is not established However it is evident that patients whose blood pressures respond to chlorothiazide will be able to enjoy salt in the diet

Sodium and Water Ratios in the Pathogenesis of Hypertension

LEO A SAPIRSTEIN

Department of Physiology The Ohio State University

The effectiveness of the low salt diet in the treatment of some cases of hypertension has prompted many investigations of the relationship between sodium and hypertensive disease Animal experiments support the general conclusions that excessive intake of sodium may induce hypertension and that hypertension induced by other means is associated with abnormally high retention of sodium within the body Lenel Rodbard and Katz[1] were able to induce arterial hypertension in the chicken by administering salt solutions Sapirstein Brandt and Drury produced hypertension in the rat by substituting 2 per cent sodium chloride for the drinking water Subsequently Masson and Corcoran[3] and Mucio *et al*[4] were able to induce hypertension in rats by substituting hypertonic saline solutions for the drinking water Extending these findings Meneely and his collaborators were able to produce hypertension growth impairment hypercholesterolemia edema abnormal electrocardiograms and widespread atherosclerosis by incorporation of large quantities of sodium chloride in the diet of rats

Many studies have suggested that the organs and whole bodies of hypertensive animals may contain excessive quantities of sodium Muscle sodium is elevated in the dog made hypertensive by the application of the Goldblatt clamp[6] most organs studied by Laramore and Grollman[7] in rats made hypertensive by subtotal nephrectomy had an elevated sodium content and a large increase in total body sodium of such rats was observed by Greene and Sapirstein[8]

The evidence for the implication of sodium in human hypertension is less complete McQuarrie *et al*[9] were able to show that hypertension developed in diabetic children after administration of very large doses of sodium chloride Epidemiologic studies of the natives of the Bahamas whose well water contains large quantities of sodium chloride show an extraordinarily high incidence of hypertensive disease[10] The high correlation between salt intake and the incidence of hypertension in man demonstrated by Dahl and Love[11] is particularly interesting

The evidence on the sodium content of the body of human hypertensives is contradictory Ross[1] has reported that intracellular sodium concentration is increased in hypertensive subjects but Moore *et al*[13] were unable to demonstrate any alterations in body sodium in a small series of hypertensive patients

More disturbing is the fact that circumstances exist in which great increases in body sodium occur in man without hypertension Healthy men can tolerate large amounts of sodium chloride without showing changes in arterial pressure though significant changes are seen in thiocyanate space and body weight[14] The edema of congestive heart failure lipoid nephrosis

subacute *glomerulonephritis* and chronic hepatitis is only occasionally associated with arterial hypertension

[11] It might be argued that the *accumulation of sodium in these circumstances is* without significance for the internal environment In each circumstance the increase in body sodium results from an isotonic expansion of the *extracellular fluid following disturbance in the relationship* between hydrostatic and colloid osmotic pressure in the capillaries Though the fluid environment of the body cells has increased in volume it has *not changed in composition It would indeed be surprising if such isotonic* expansion of the extracellular fluid were to induce the vascular responses which result in hypertension

Yet *if isotonic loading with sodium chloride does not in itself* produce the hypertensive state we must inquire why hypertonic loads of sodium chloride which do induce hypertension are not made isotonic and thereby *ineffective The question can be rephrased If in fact* hypertension is associated with excessive retention of sodium why is it not followed by retention of water and so converted into an extracellular edema?

[F] The conversion of a load of sodium chloride from a hypertonic to an isotonic one requires osmoreceptors capable of detecting the abnormality in the osmolarity of the body fluids produced by the hypertonic load a supply of water *sufficient to adjust the osmolarity of the loading solution* and kidneys capable of preserving the iso osmolar state once it is attained during periods when water is not being taken by the organism Disturbance *in any of these may result in failure to maintain iso* osmolarity when the body is challenged by either the administration of osmotically active solutes or the deprivation of water Such failure would result in alteration of the composition *rather than the volumes of the body fluids Although* admittedly the mechanism through which such alterations would induce vasoconstriction are not known it seems reasonable to assume that vascular *reactivity and resistance* would be *more readily influenced by changes in* the composition than by changes in the volume of the body fluids

At the present time no evidence is available to indicate that the osmoreceptors *function abnormally in the hypertensive* That hypertension may be induced in situations where water shortage limits the possibility of osmotic adjustment is illustrated by the results of those studies already cited in which *hypertonic salt solutions are substituted* for the drinking water [14] The drinking which results from the disturbance of the osmolar status of these animals does not correct but indeed exaggerates the osmolar disturbance

Prejudice to the control of osmolarity can also occur even when ample water is available to cover an osmotic load and the osmoreceptors are functioning adequately *if the kidneys are not capable of preserving* the osmolar status between drinks of water *If* for example the kidneys continually eliminated a hypo osmolar urine while the body fluids were intermittently brought to *iso osmolarity* by *taking* water the animal so afflicted would at almost all times be somewhat hyperosmolar

Even when the kidneys are capable of producing hyperosmolar urine they may still fail to meet the *requirements* of osmolar homeostasis The preservation of body osmolarity requires that the kidney *eliminate a urine* whose osmolarity corresponds to the load on the body fluids of ingested and

metabolically produced solutes dissolved in the ingested and metabolically produced water Further the kidney must make good losses of "free water"* in excess of osmotically active solutes by way of the skin lungs and alimentary tract It is obvious that the mere fact that hyperosmolar urine is produced by the kidney does not guarantee that the kidney has functioned adequately in osmoregulation Only when the renal production of "free water" keeps pace with "free water" losses can the kidney be considered to be defending the osmolarity of the body adequately

It has long been known that the ability of the kidney to conserve water is impaired in hypertension [16] Though the hypertensive kidney can elaborate a hyperosmolar urine under conditions of osmolar loading its water economy (free water saved for the body) is less than normal [17] The water saved for the body with respect to either sodium or chloride is less in hypertensive than in normal subjects [18, 0] The hypertensive eliminates these ions as fast as or faster than the normal subjects but in doing so he uses more water

The same finding has been noted frequently in experimental hypertension Oster and Martinez [1] described the profound polyuria and polydipsia of hypertensive rats Braun Menendez noted that hypertensive rats excreted chloride as rapidly as normals but with much larger volumes of water Ezrow and Sapirstein [3] found that hypertensive rats whether under basal conditions or loaded with hypotonic isotonic or hypertonic sodium chloride solutions excreted the sodium ion as well as the normal controls but always during this excretion they eliminated more water than the controls

Although it seems clear that there is a potential abnormality in osmolar regulation in the kidney of the hypertensive it is not clear whether the deficiency is sufficiently great to prejudice the body s control of osmolarity in normal circumstances it may be revealed only in the presence of exceptionally heavy osmotic loads Little work has been done on this point but the finding that the level of urinary antidiuretic hormone is elevated in human and animal hypertension [4] suggests that the control of body osmolarity may be significantly impaired in the normal conditions of life The fact that plasma sodium concentrations are slightly elevated in hypertensive animals and in men [9, 27] may indicate that a water deficit rather than a sodium surfeit exists in hypertension

The findings which have been presented may be summarized in the following statements Certain conditions which increase the osmolar load on the body (hypertonic loading with sodium chloride) as well as other conditions which tend to impair the ability of the kidney to correct hyperosmolarity of the body fluids (diminished ability to produce "free water") are associated with arterial hypertension Furthermore arterial hypertension in both men and animals appears to be associated with slight but potentially significant elevation in the concentration in the body fluids of the osmotically significant sodium ion

Evidently these findings do not prove the existence of a causal relationship between hyperosmolarity of the body fluids and arterial hypertension

* As used here and subsequently the term "free water" refers to the amount of water which must be removed from a solution to bring it to iso-osmolarity A negative sign of free water implies that water must be added to the solution to make it iso-osmolar i e that the solution is hyperosmolar A kidney which produces a hyperosmolar urine has in doing so conserved free water for the body The term is used in the same manner in which it was employed by Wesson and Anslow [15] in description of the urine

However it does not appear unreasonable to postulate as a working hypothesis that such a relationship may exist

This working hypothesis would imply that an excessive consumption of sodium chloride can induce the hypertensive state if and only if there is at the same time a failure to adjust body water to body sodium In this view the intake of sodium is of less importance than the relationship between sodium balance and water balance Abnormal metabolism of water—for example excessive losses of free water in sweating or habitual disregard of thirst—may be more significant in the pathogenesis of hypertension than abnormal intake of the sodium ion In the same way it is quite conceivable that the favorable effects of the low salt diet are more directly referable to the removal of the osmolar load on the body water than to any specific effect of sodium

Perhaps the most intriguing aspect of the proposed hypothesis is that if it is correct it may add an important new substance to the medical armamentarium against hypertension—water If the basic deficiency in hypertensive disease is hyperosmolarity of the body fluids generated either through renal inability to save "free water for the body or through inadequate intake or excessive loss of "free water" or through any combination of these the rational remedy would appear to be increased consumption of tap water To my knowledge there have been no studies made on this point

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Hypertension and Stress

LEWIS C MILLS

Hahnemann Medical College and Hospital

The role of the kidney the adrenal cortex and medulla certain enzymes hepatic factors trace metals various humoral agents and salt and water metabolism in the etiology of hypertension are discussed elsewhere in this symposium While the evidence is adequate to support the participation of one or more of these factors in various hypertensive states the evidence is not clear as to the nature of the initiating or precipitating factor in the group of patients with essential hypertension Experimentally such changes are initiated by the investigator but what factors lead to the development of non nephritic renal ischemia adrenal secretory abnormalities abnormal metabolism of sodium and water increased vascular sensitivity or abnormal secretion of humoral hypertensive substances in naturally occurring essential hypertension? Examination of the physiologic and metabolic responses to various types of stress suggests a way in which such changes could be initiated and evidence has already been presented to indicate that hypertension can be maintained even though the initiating factor is no longer operating

EFFECTS OF STRESS ON BLOOD PRESSURE

The effects of stress on blood pressure have been documented in several studies Experimentally in animals psychic stress may cause hypertension in one study emotional excitement induced in cats by hostile dogs led to hypertension in 50 per cent of the animals This was associated with cardiac hypertrophy and slight evidence of renal damage[1]

Imhoff *et al*[2] presented normal and hypertensive subjects with a series of mathematical tests and also had the subjects speak on topics relative to themselves Blood pressure was temporarily increased in the majority although in many the rise was small and transient Hypertensive patients reacted qualitatively like the normotensive but the response was greater It was also of interest to note that the intensity and duration of the response increased with age since there is an increasing incidence of hypertension in older age groups These observations were interpreted to indicate that adaptive mechanisms were slowed in older people

Other workers have also noted the effects of psychic stress or stressful interviews in normal and hypertensive patients[3 10] Hypertensive responses were correlated to psychic responses in which the subject felt menaced or trapped and were due to increased peripheral vascular resistance with a normal stroke volume and pulse rate as in patients with essential hypertension if on the other hand subjects were overwhelmed blood pressure tended to fall[9] These observations were compatible with analyzed personality patterns of hypertensives who were noted to be "mobilized for combat but who did not or could not take action Moses *et al*[11] noted that rage and

resentment were the predominant psychologic manifestations of patients with severe hypertension (blood pressure > 160/100) Subjects with minimal hypertension had anxiety syndromes again with minimal overt expression and had the same although less marked alterations in cardiovascular hemodynamics

Three patients were observed in whom malignant hypertension suddenly developed in relation to major catastrophic events" These patients had spent years in successfully developing their vocations but failed to be promoted in terms of security money and position This led to enragement and a feeling of being trapped and presumably to the onset of hypertension

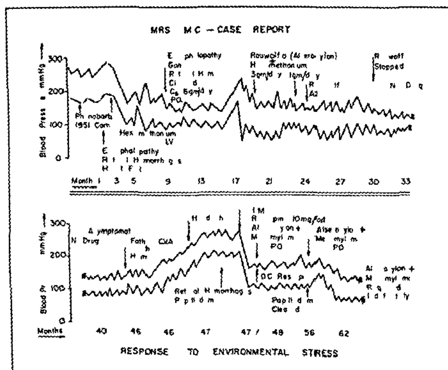


Fig. 1 Recurrence of severe hypertension after emotional stress in a patient previously controlled with drug therapy See text

That so-called "labile hypertension" commonly observed to result from mild to severe emotional crisis is often followed by sustained essential hypertension is amply shown by the studies of Levy *et al*[1] Their analysis of case records of military personnel revealed that during the period of observation only 2 per cent of originally normotensive patients developed sustained hypertension whereas 31 per cent of those having "transient hypertension (blood pressure of 150/90 or greater with subsequent normal values) developed a sustained elevation of their blood pressure Subjects developing sustained hypertension appeared to be clinically indistinguishable from those with essential hypertension and some developed classic cardiovascular renal complications during the period of observation

More persistent "transient hypertension" has also been observed due to

stress Of 695 men exposed to the stress of combat[13] diastolic hypertension occurred in 27 per cent (diastolic pressure greater than 100 mm of mercury) This persisted in some subjects as long as one to two months after leaving the combat zone Ruskin et al[14] noted diastolic pressures greater than 95 mm of mercury in 57 per cent of victims of the Texas City disaster In his patients elevations persisted for one to two weeks after the stressful stimulation

In further support of the role of emotional or cortical stimuli in the pathogenesis of hypertension are the occasional observations that psychotherapy[11] topectomy[15] leucotomy[16] and lobotomy[17] may convert patients from a hypertensive to a normotensive state when the procedure results in a change in the patient's mental attitude Indeed to anyone who has had experience in the treatment of patients with hypertension the effects of

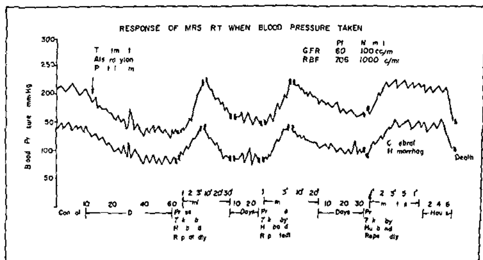


Fig 2 The effect of emotional stress on blood pressure resulting eventually in cerebral hemorrhage See text

emotional stress are well known and all agree that such stimuli are capable of causing further elevations in blood pressure

The patient whose blood pressures are presented in Figure 1 had severe malignant hypertension when first seen The hypertensive state was controlled during the first year with hexamethonium and later by a combination of hexamethonium and alseroxylon During the second year it became possible to decrease the dose of hexamethonium and finally to discontinue it after the thirtieth month all antihypertensive drug therapy was stopped During the next year and a half blood pressure remained at the upper limits of normal At this time the patient's father had a cerebrovascular accident The patient was closely attached emotionally to her father and was noted to be more than usually distressed after this event In the succeeding few weeks her blood pressure rapidly increased to levels averaging 280/230 This was associated with retinal hemorrhages papilledema and headaches Although it was possible to control the hypertension again with drug therapy it has not been possible to discontinue it although treatment has been continued for over two years Although the recurrence of hyper

tension may have been coincidental with the father's illness close observation of this patient's course and emotional situation over a seven year period suggests strongly that the emotional stress was the precipitating factor

The direct effects of emotional stress on the blood pressure of one patient are presented in Figure 2 This patient had moderately severe hypertension averaging 205/140 during an initial control period During therapy with a ganglionic blocking agent and alseroxylon the blood pressure fell to an average of 135/85 The patient's husband was then instructed in taking the patient's blood pressure at home This led to considerable emotional stress in the patient and was associated with marked rises in her blood pressure to levels as high as 225/135 During one of these episodes when the pressure was being taken the patient had a cerebral hemorrhage and died a few hours later

The blood pressures of another patient in whom hypertension was ag-

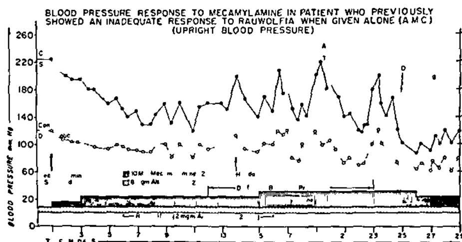


Fig 3 The effect of business problems (emotional stress) on blood pressure See text (From Moyer *et al* Drug Therapy (Mecamylamine) of Hypertension A M A Arch Int Med 98 187 1956)

gravated by emotional stress are presented in Figure 3 This patient also had severe hypertension and failed to respond to Rauwolfia alone With the addition of mecamylamine satisfactory control was obtained (blood pressure averaged 140/95) At this point he had to cope with difficult business problems for a period of eleven days During this interval there were rises in blood pressure to levels as high as or higher than the pretreatment values in spite of increased dosage of mecamylamine When his emotional stress was relieved by solution of his business difficulty his blood pressure promptly fell to levels of 100/70 with postural dizziness necessitating reduction of the dose of mecamylamine

The data cited above clearly indicate that psychic stresses can produce transient hypertension and can aggravate existing essential hypertension These observations also suggest that such stress may be a primary etiologic factor in at least some patients with essential hypertension To be explained are the mechanisms by which stress can initiate hypertension and how such an etiology can fit in with the observed abnormalities in essential hyper-

tension. It is well known that emotional stress can affect both the vasomotor centers and the hypothalamic-pituitary axis. As a result of this stimulation a number of potentially hypertensive reactions could be initiated. Some of these are presented in Figure 4.

EFFECTS OF STRESS ON THE AUTONOMIC NERVOUS SYSTEM

The effects of stress on the autonomic nervous system are manifest in response to emotion, trauma and other stimuli. Both parasympathetic and sympathetic functions may be affected depending on the type of stress, resulting in characteristic and well known manifestations. Those of increased

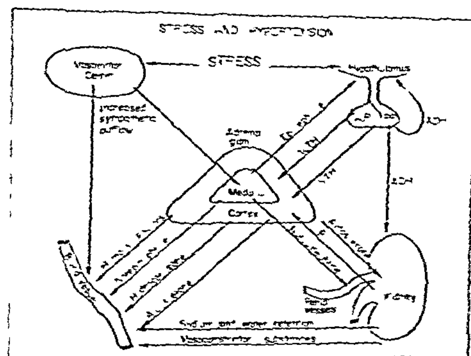


Fig. 4. The relationship of stress and hypertension. See text for discussion.

sympathetic function include increased blood pressure and variable changes in cardiac output, stroke volume, pulse rate and peripheral resistance, and this is confirmed by the finding of increased amounts of urinary catecholamines.

EFFECTS OF STRESS ON ADRENAL MEDULLA

The effects of stress on adrenal medullary function ... the sympathetic nervous system and result in increased ... rine and norepinephrine as evidenced by chemical ... and creased excretion of these substances in ... bearing is the evidence that secretion ... ays constant proportion. This probably ...

diac output and pulse rate in relation to blood pressure response cardiac output being increased when epinephrine secretion is predominant and little changed when norepinephrine predominates Further the tolerance of pilots to the vascular (and emotional) stress of increased gravity can be correlated with urinary excretion of norepinephrine and epinephrine high levels of norepinephrine occurring during high "g" tolerance and an aggressive hostile attitude and increased levels of epinephrine with low tolerance and acute anxiety [1] This response could be modified in the same subject by appropriate "psychotherapy" by the psychiatrist These data are of particular interest since they correlate closely with the observed cardiovascular hemodynamic changes produced when various emotional states are induced in normal subjects i e a tendency to increased blood pressure due

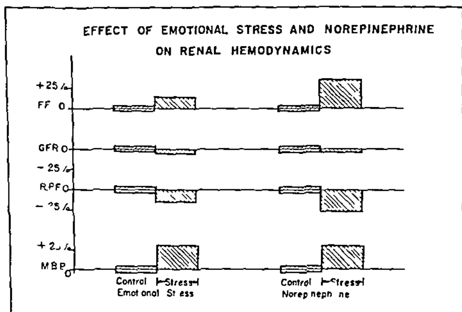


Fig 5 Comparison of the effects of emotional stress and norepinephrine infusion on renal hemodynamics Note that changes are qualitatively similar (The data on stress effects were adapted from Pfeiffer and Wolff J Clin Invest 29 1227 1950)

primarily to increased vascular resistance when a hostile response was elicited (norepinephrine type response) and tachycardia increased cardiac output and little change in blood pressure when an anxiety reaction was induced (epinephrine type response) Since small amounts of norepinephrine may cause an elevation of blood pressure with few if any associated clinical signs this could be an operating factor in beginning essential hypertension

EFFECTS OF STRESS ON RENAL FUNCTION

The effects of stress on renal function have been studied by several investigators Injection of India ink into the renal vessels of normal cats and those stressed by confrontation with a barking dog revealed decreased renal

cortical circulation in the stressed cats Electrical stimulation of cerebro cortical pressor areas [3] and painful stimuli [4] have also led to renocortical ischemia

Emotional stress in normal and hypertensive humans may lead to diminished renal blood flow [6 7 8] In such instances renal blood flow may decrease to 75 per cent of control values accompanied by a slight decrease in glomerular filtration rate and an increase in the filtration fraction and renal vascular resistance In sympathectomized patients the response was modified efferent arteriolar constriction did not occur while afferent arteriolar constriction was unchanged suggesting that both neurogenic and humoral factors were operating in nonsympathectomized patients Such renal hemodynamic responses are probably not characteristic of a given stimulus but it is of interest that similar alterations can be produced in humans by infusion of norepinephrine (Fig 5)

Stress may also influence urine volume and electrolyte excretion Unpleasant stimuli and fright due to sounding of an automobile horn [6] have led to antidiuresis in dogs and Verney [7] has shown that emotional stress may cause release of antidiuretic hormone Sodium may be retained as a result of both emotional[26] and traumatic stress (bone fracture) [8] In the latter experiment there was increased potassium excretion probably indicative of adrenal cortical activation

EFFECTS OF STRESS ON PITUITARY FUNCTION

The effects of stress on pituitary function and therefore presumably on hypothalamic function have been demonstrated Adrenocorticotropic hormone is released by stress [29] frustration due to forced restraints being particularly effective [30] Increased amounts of somatotrophin may be released during stress [31] and as noted above there may be increased release of antidiuretic hormone [27]

EFFECTS OF STRESS ON ADRENAL FUNCTION

The effects of stress on adrenal function are also well documented In surgical or traumatic stress [3 33] well marked easily detectable changes occur There are large rises in plasma and urinary 17 hydroxycorticoids Characteristic negative nitrogen balance retention of sodium and water potassium excretion and many other metabolic changes occur

In emotional and psychic stress adrenal activation has been more difficult to demonstrate and many studies have shown negative results However since the development of more refined techniques for measuring plasma ACTH hydrocortisone and urinary corticosteroids such changes have been demonstrated in response to a number of different types of psychic stress Urinary 17 ketogenic steroids increased significantly in eight subjects repeating an examination in which an unsatisfactory outcome meant a marked reorientation of their vocational outlook[34] Urinary 17 hydroxycorticoids were increased in the urine of members of a crew racing team on days of timed practice and on the day of the actual race but on days of nonemotionally stressed rowing (i e nontimed practice) urinary excretion was not significantly different from days on which rowing was not done [35] suggesting that psychologic stress was the important determinant Adrenocortical

steroids have been noted to increase in response to emotional arousal characterized by anxiety of a disintegrative nature[36] in students during college exams[37] in psychiatric patients on admission to a mental hospital[38] during anxiety[39] during stressful life experiences[40] in disturbed schizophrenics and patients with other mental disorders[37] and in response to frustrating psychologic tasks[41] Such changes in response to emotional stress are often subtle difficult to detect and within normal physiologic ranges although when viewed in relationship to suitable control determinations and analyzed statistically are highly significant

MECHANISM BY WHICH STRESS MAY PRODUCE OR AGGRAVATE HYPERTENSION

This is still not completely clear but as noted above there is ample proof that stress of an emotional nature does stimulate the central sympathetic centers hypothalamus and pituitary Increased sympathetic activity could lead to direct arteriolar vasoconstriction including the renal arterioles as well as to stimulation of the adrenal medulla to secrete increased amounts of epinephrine and norepinephrine into the circulation which in turn would cause vasoconstriction Renal vasoconstriction could lead to renal ischemia with resultant liberation of renin or other vasoconstrictor factors Renin in turn might act on the adrenal cortex with resultant secretion of additional humoral vasoconstrictor factors or substances increasing vascular sensitivity to vasoconstrictor impulses or humoral agents Secreted epinephrine in addition to its vascular effects may stimulate the hypothalamus and pituitary gland[4] although its role in human hypothalamic pituitary function is not yet clear Thus stimulation in combination with stimuli descending through cortical hypothalamic or other central pathways as a result of stress could lead to secretion of ACTH which in turn would stimulate adrenal cortical secretion of hydrocortisone and other steroids This could lead to renal sodium and water retention and perhaps to a sensitization of vascular smooth muscle to vasoconstrictor agents Secretion of somatotrophin may also be increased it has been suggested that this may be one factor regulating adrenocortical secretion of aldosterone[31 43] The latter would tend to increase renal sodium and water retention and might have a direct cellular effect on the ratio of intracellular to extracellular potassium or other electrolytes thereby increasing vascular reactivity Somatotrophic hormone may also sensitize vascular tissues to the effect of mineralocorticoids[43] In addition renal damage including nephrosclerotic-like lesions can be produced experimentally by administration of somatotrophin in some way which may not be related to mineralocorticoids but related to adrenal integrity since the damage is prevented by adrenalectomy even though replacement therapy is given[30] Antidiuretic hormone is also released in stress This could potentiate water retention

CONCLUSIONS

An analysis of these interrelationships is consistent with much of the data relating to naturally occurring human hypertension In addition it is consistent with the known action of various hypotensive drugs used in the treatment of hypertension Agents which act centrally such as hydralazine

diminish sympathetic outflow while reserpine and chlorpromazine probably decrease sympathetic outflow and reduce hypothalamic pituitary function Other agents such as ganglionic blocking drugs or adrenergic blocking drugs block the sympathetic nervous system peripherally Hydralazine may also act by reducing vascular sensitivity locally Amphenone or aldosterone antagonists block the adrenocortical response locally or at the renal tubular level and diuretics and sodium restriction counteract the effects of sodium and water retention

It would seem that if essential hypertension were primarily on the basis of a local renal defect and ischemia or a renal enzymatic defect leading to increased secretion of renin or other vasopressor agents there would be diminished sympathetic tone and therefore little response to either centrally or peripherally acting sympatholytic drugs Similar arguments may be advanced if one considers any single peripheral factor as the primary cause This suggests that there are multiple abnormalities present in essential hypertension and that these most likely occur as a result of central nervous system stimulation while any one abnormality might not be of sufficient magnitude to be hypertensive in itself a combination might be synergistic Such changes would be difficult to detect by conventional laboratory methods and when detected might be significant only when viewed in the light of the total abnormalities—for example in the case of increased adrenal activity in response to emotional stress it has been only recently that these changes could be detected Furthermore patients classified as having essential hypertension may be a heterogeneous group in which there is a greater sympathetic hormonal electrolyte or other abnormality in one patient as compared to another this would make statistically positive correlations almost impossible That such a possibility is likely is suggested by the group of patients with essential hypertension reported as having an "endocrine hypertensive syndrome"[44]

Although a convincing case can be made out for the role of stress in the etiology of essential hypertension the evidence to date is primarily circumstantial (but no more so than any other suggested etiologic possibility for essential hypertension in humans) and much further work is necessary to prove this or any other possibility However there is no doubt as emphasized elsewhere in this symposium that emotional stress can and does aggravate existing essential hypertension

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Discussion

William A Sodeman *Moderator*

A C Corcoran	George Meneely
J Richard Crout	Lewis Mills
Lewis Dahl	Leo Sapirstein
Robert Gaunt	Henry Schroeder
Arthur Grollman	Sheldon Sommers
Phyllis Hartroft	Mordochai Toor
G M C Masson	George Wakerlin
Milton Mendlowitz	

Dr Sodeman Dr Meneely in your discussion on the effects of feeding salt you didn t go into any of the mechanisms whereby you thought this might produce hypertension How do you stand on some of the explanations of what you found?

Dr Meneely I would like to comment on some of the observations on total body sodium and exchangeable sodium and potassium I m not sure that you know very much when you know the exchangeable sodium It has never been clearly established what the relation of exchangeable sodium is to total body sodium and the same is true for potassium The total exchangeable potassium is tricky as a technical proposition because of the different equilibration times in different systems but those data shown were in accord

with what we *found in rats* We were surprised to find in our rats that the total exchangeable sodium and the exchangeable potassium are not much changed and such changes as we did find were paradoxical In a rat on very high salt intake and relatively low potassium intake the total exchangeable potassium was up not down which is the opposite of what you would predict It's been known *for a long time that exchangeable sodium in the so called sodium space is not significantly* altered in essential hypertension *Perhaps Dr Sapirstein's* explanations in relationship to water may be in the right direction However he didn't say very much about renal adjustment of these affairs which seems to be under pretty good regulation usually by steroid mechanisms

DR SAPIRSTEIN There are a number of points I would like to make I think that it has been pointed out that it would be nice to have a mechanism with which sodium excess would in fact induce hypertension I remember the findings of Ellis and Grollman some years ago in which it was shown that *the antidiuretic hormone* was *considerably increased in both the plasma and* the urine of essential hypertension I wonder if another antidiuretic hormone might be released into the circulation There are a couple of points that I did not have time to make before There is evidence in human subjects to indicate that sodium concentration in serum or plasma is distinctly elevated *The findings show an elevation of something like 7 or 8* per *cent in serum sodium* in hypertension As regards Dr Meneely's question about the renal regulation of the sodium water ratio I believe the kidney does a pretty good job but I'm inclined to think that one of the first evidences of renal failure is its inability to accomplish the osmotic regulation required to keep sodium and water *in proper proportions to each other in the body It's* quite clear that the kidney cannot conserve as much water through the body in hydropenic hypertensive man as in the normotensive There is a very distinct limitation in the concentrating ability which perhaps may be at fault

DR GROLLMAN We have been dealing with well established facts in most of the discussion this afternoon Apparently as Dr Meneely showed if you administer salt long enough in large doses to rats you get hypertension Dr Dahl and Dr Sapirstein presented convincing evidence of a relationship *between the sodium intake and hypertension I would differ however* from certain inferences that have been drawn as to the bearing of these observations on the pathogenesis of hypertension Hypertensive disease is a systemic disorder It involves many tissues and it's not surprising therefore that if you analyze these tissues you find some deviation from normal as *regards their sodium potassium and water content A* severe dislocation of electrolyte and water balance may induce changes which will result ultimately in hypertension.

As regards the relation of stress to hypertension instead of having a number of facts here we have a lot of theories and fictions which we accept because they *soothe our vanity* There is no good evidence to support the idea that stress causes hypertension Both the experimental studies on animals as well as the available clinical data fail to support such an assumption In none of the sessions this morning despite the many attempts made to do so was any evidence brought forth to show that there was any extra epi

nephrine in the body in the hypertensive or extra serotonin, or extra aldo sterone or any other agent concerned in stress

DR MENEELY Our rats have personality changes This was drawn to our attention by our technical people who found that our high salt eating rats are irascible and exhibit a good deal of frustrated aggression and are really rather trying to deal with I suspect that it s the salt they re eating and the high blood pressure they get from it that produces the personality changes because they don t have any choice about whether they eat salt or not

DR SODEMAN Do you study them on the couch or under it?

DR SAPIRSTEIN I m interested in what Dr Grollman had to say particularly about the substances which may or may not be circulating in the blood of the hypertensive individual and which may or may not have a causal relationship to hypertension I don t think that we should dismiss lightly those substances especially when they may have a role in the maintenance of hypertension Now am I to understand Dr Grollman that you believe that the circulating antidiuretic hormone be regarded as ultimately insignificant?

DR GROLLMAN No I didn t say that I said that it represents a part of the over all change There are probably many other differences between the normotensive and hypertensive no one of which is necessarily concerned in the pathogenesis or essential for the maintenance of hypertension

DR SAPIRSTEIN Well the question I had chiefly in mind was this Do you think that the quantities of antidiuretic hormone which you found in the hypertensive were sufficient so that they might be considered to have an etiologic role in the maintenance of an elevated blood pressure?

DR GROLLMAN No I look upon it merely as one of the changes occurring in the hypertensive without assuming that it acts on the brain or the kidney or other tissue to cause hypertension

DR. CROUT Having discussed the sympathetic nervous system this morning I d like to clarify a couple of points One is that I disagree with Dr Grollman that there is no relation of stress to the blood pressure I think it is amply documented in the studies of Wolf and others in their book *Life Stress and Hypertension* In both normals and hypertensives a variety of stresses may decrease renal blood flow and elevate the blood pressure Certainly every clinician is aware of the fact that once hypertension is established stress profoundly influences his patient So we should separate whether stress participates in the pathogenesis of the disease or whether it s an aggravating factor I don t think there is a great deal of disagreement that stress is a profound aggravating factor in the established disease

DR GROLLMAN Everyone knows that stress stimulation of the sympathetic nervous system and epinephrine raise the blood pressure But do repeated pressor stimuli induce chronic hypertension? That is the crucial point

DR TOOR We assume that in essential hypertension there is some specific factor involving sodium excretion and sodium load This was accepted knowledge for years and we tried also to correlate this with the pathogenesis of essential hypertension I tried yesterday to make it clear that intraventricular hypertension in aortic stenosis occurs without systemic hypertension despite the same pattern of sodium excretion seen in essential hypertension It is very hard to assume that the changing pattern is specific to essential hypertension As I indicated yesterday we see it also in pulmonary hypertension and in pulmonic stenosis where there is only right intraventricular hypertension Hence this form of sodium metabolism cannot be assumed to be the specific factor of essential hypertension I was interested to hear Dr Meneely mention electrocardiographic changes with increase in sodium intake Were there also changes in the blood sodium?

DR MENEELY No the plasma sodium levels stay right at normal

DR MENDLOWITZ Dr Sapirstein made very rapid calculations of Dr Winer s data and came up with the idea that sodium concentration in Dr Winer s cases was higher in the hypertensives I go along with Dr Sapirstein in his renal hypertensive rats but I think it s a little bit dangerous to extrapolate that type of thinking to human hypertensives in the presence of data like those which Dr Winer presented

DR WINER With reference to serum sodium in my study there was no difference at all between the normal and the untreated uncomplicated hypertensive group This was in contrast to several papers in the literature on serum sodium but if you examine those papers there is a difference between their studies and mine They included patients with severe hypertension including malignant hypertension in which there are many factors involved In my study there was clearly no difference at all relating sodium potassium plasma and extracellular water to total body water I had anticipated that there might be if sodium were involved pathogenetically We might be missing an intracellular change if we can extrapolate our data but this is certainly not the same as measurements of intracellular sodium The experiments of Tobian cannot be used to indicate a high intracellular sodium since these patients were very sick hypertensives No statements were made about edema With reference to exchangeable sodium this is that amount of sodium available as a pool It has been studied and found that bone sodium is not completely exchangeable I think about a third of bone sodium is exchangeable the rest is not The rest of the body sodium is exchangeable so that we re picking up a good proportion but not all body sodium In primary aldosteronism and periodic paralysis exchangeable sodium is found to be high even when related to body weight

Dr Toor makes the point that these changes in salt excretion after salt load may be referable to a mechanism of intraventricular pressure and that this would occur in any kind of hypertension This gets substantiation in the literature in multiple ways of an indirect sort I believe that this increase of salt excretion after salt load occurs in diverse forms of hypertension steroid hypertension renal hypertension as well as essential hypertension So it is not peculiar at all to essential hypertension and would not

therefore be considered in any way primary In addition there have been a few studies on a change in salt excretion after salt load which correlates with the height of blood pressure and which changes in association with changes in the blood pressure Again this would indicate perhaps a secondary phenomenon

DR MENEELY I think it s terribly important first to distinguish between what is clearly fact and what may constitute interpretation I think very few people would argue with the notion that if you push enough sodium chloride into almost any animal including a human it will make him hypertensive There is some argument as to what the levels are but there isn t any argument about the fact that it can be done There isn t any argument about the fact that potassium salts have powerful protective effects There is a lot of argument about modus operandi The fact that we don t understand why something happens is not a reason that it doesn t happen when it does When you increase the sodium chloride intake the animals will increase their water intake It is perfectly within the realm of possibility that the increased water intake might be the cause of the hypertension not the sodium This has never been ruled out

DR WAKERLIN Dr Grollman spoke of the fact that so far as he knew hypertension had never been produced experimentally in animals by stress I heard from Dr William Dock very recently that a successful experiment has been done in Russia the experiment consisted in placing three male monkeys in the same cage with one female monkey and then after a period of several months a screen partition was made and two of the males were in a separate cage but clearly could see the other male and the female Over a period of several months both of the frustrated males developed considerable increases in blood pressure and these persisted throughout the period of observation which was according to Dr Dock about 12 months Now of course the most important part of this experiment hasn t been reported upon—what happened after the male monkeys were no longer frustrated Was this an experience similar to that of British soldiers at El Alamein or of people in the Texas City disaster when blood pressures went up and stayed up after a very severe stress for a period of some months or weeks and then came down? I think that by and large Dr Grollman is still correct but maybe using the chimpanzee will get us closer than using the rat or the dog for this kind of experiment

All human beings are stressed at one time or another but not all human beings develop hypertension If the stress mechanism should operate for example through renal vasoconstriction with the setting off of a renal pressor mechanism which is one possibility then it is clear that renal vasoconstriction occurs in the people who do not develop hypertension except perhaps on a temporary basis There must be some latent biochemical lesion in the kidney or in other organs which originates the hypertension and this of course is extremely important for us to find out so that basically the stress mechanism then would be a trigger mechanism but the primary mechanism would be something else And this is I think what we are especially interested in

Finally if I might say a word about sodium here I think it is possible that all of the things that we have been talking about this morning and this

afternoon might operate through alterations in sodium metabolism or the amount of sodium outside the smooth muscle cell membrane and the amount *inside the smooth muscle cell membrane as a common denominator* and if this should some day be found out to be the case then all of us are right

DR CORCORAN There is an early phase of essential hypertension in which there is no particular vascular disease and characteristically *in those people* there is no renal vasoconstriction in the sense that there is no decrease in renal blood flow There is an *increase in renal vascular resistance* but there isn t anything comparable to that induced by fright putting your hands or feet in cold water or by noradrenaline—*so that if this peripheral adrenergic* sort of thing that has been postulated were a pathogenic mechanism one should see adrenal vasoconstriction which is active and which has a high glomerular filtration fraction in very early hypertensive disease One does not see that Therefore I would tend to discount this as a primary influence and go back to the position that it may be more than permissive but less than pathogenic

DR SAPIRSTEIN It seems to me that at the Wistar Institute hypertension was induced by audiogenic seizures many years ago

DR GROLLMAN We have repeated these experiments Although the blood pressure of the animals rises during the seizures and many die in convulsions they do not develop a chronic elevation in blood pressure or the other characteristic changes observed in hypertension

DR SCHROEDER About this stress thing A number of years ago I wrote a review on hypertension which started with the words Essential hypertension is a psychosomatic disease" I would like to take that back I ve had a lot of fun lately developing a theory that it may be somatopsychic disease starting in the kidney and producing cerebral symptoms We know from psychological studies that emotional tension is common in hypertension and *in psychoneurosis* There are three people sitting here that I know of who have made the observation that emotional tension disappears in the treated hypertensive patient *Dr* Smirk has made the same observation and I think it s a very striking thing when you know your patient well to realize that his *tension goes* when you give him drugs which presumably have nothing to do with his brain and I m not talking about Indian snake root—I m talking *about more potent drugs I think that* it s possible that the kidney does as Dr Wakerlin says bother about chemical abnormality which makes the *person tense and which may make him respond to stress more than he ordinarily would* perhaps

Now *if I might say something* about Dr Meneely As I saw his blood pressures on the 2 8 per cent salt or 14 gm equivalent for man they were *not impressively elevated I m not sure whether they* were statistically elevated but 126 I believe was the mean systolic pressure which is not par*ticularly high in the rat, although it climbed up* when you got to 28 gm or 52 gm Any doses above 14 gm are pretty unphysiologic

I d like *to ask Dr Dahl if he would talk about these* high salt eaters in the northern part of Okita and Naomon prefectures in Japan where the *stroke rate is over twice that in the southern prefecture* They are rumored

to take up to 25 to 30 gm of salt a day and they do have more hypertension although the report is that those who live on the sea coast eat as much salt but eat seaweed which protects them from their hypertension but that I don t know about

DR SAPIRSTEIN As Dr Corcoran suspected I didn t have time to do the statistics on Dr Winer s data However until he makes the calculations I suspect that the difference would turn out to be significant I just want to ask one further question about the measurements of total exchange of the sodium Are your results consistent with those of Ross?

DR WINER Ross published a paper in the Lancet about two years ago in which he showed that patients with hypertension possibly essential hyper tension I am not sure did have high values He also showed many patients who had normal values He showed a scattergraph in which he plotted the funduscopic picture vs the exchangeable sodium His high exchangeable sodiums were his grade 3 and grade 4 fundi They were not in the grade I and grade 2 fundi

DR MENEELY To answer Dr Schroeder s point the 2 8 per cent salt eating rats do have a higher blood pressure than those at the control level Those data of course that I showed you were only at 9 months the difference becomes greater as time goes on but even then it s already significant

DR CROUT I suppose we shouldn t let the afternoon pass without at least commenting on the adrenal medulla seeing that it s half the gland and we paid no attention to it I rather think this does reflect its importance I don t want to dwell on the obvious but we should note that adrenal epinephrine may produce large changes in the potassium mobilization and there are some modest changes in excretion of sodium and water as well as a host of other metabolic and vasoactive effects Nonetheless these are all reported in animals with doses a great deal higher than the human has apparently been subjected to from his own endogenous production and I rather feel that this should not be extrapolated beyond this particular experiment in the animal in which they were done The adrenal medulla is always placed on graphs that show the pituitary and its various mechanisms of action but I think the evidence that it really does anything in man is pretty poor

DR DAHL I would like to add one note about total exchangeable sodium We reported this originally in 1951 and found no change in hypertensives I have now done it on some 75 people under a wide variety of conditions and although I was aware of Ross s paper I have not really felt that it was worth while to spend my time writing a paper to the contrary but I think the evidence is quite unequivocable that hypertensives in all stages—unless failure has supervened—have normal total exchangeable sodium Relative to the question of Dr Schroeder about the Japanese in Okita and other pre fectures in Japan who have a very high salt intake (one person ingested 55 gm a day) the fact of the matter is that the people on the sea coast who have less hypertension eat less salt since they eat fresh fish I think the evi dence is quite unequivocable that the people in the prefecture where hyper tension is very frequent and cerebrovascular accidents are very common

have a very high salt intake Relative to water and salt we have at one stage of our career forced fluids up to 4500 cc per day on people with both low salt and high salt intakes under metabolic ward conditions which kept them busy both drinking and voiding We found no effect on anything except their activities pertaining to voiding

Dr Schroeder We seem to agree pretty much that clinically salt restriction lowers blood pressure in the severely hypertensive patient Those of us who had nothing else to treat hypertensives with but severe salt restriction were often disappointed by the poor results that we got with severe salt restriction or the rice diet I think Dr Dustan and Dr Corcoran would agree with me that certainly salt restriction is by no means a panacea for hypertension under the most ideal conditions and where the patient is carefully controlled

Dr Mills In regard to the comment that was made that patients are frequently observed who are quite stressed but don t have hypertension I think it is certainly well recognized that people react in different fashions to stress For example in military personnel exposed to combat some may react with the emotional situation that we know as combat fatigue I m sure that some of them do react with temporary hypertensive episodes Personnel exposed to the stress of a centrifuge or gravity stress will react to the same amount of stress in different fashions depending on what their emotional attitude is at the time the stress occurs If they have an aggressive attitude toward it they can withstand quite a high gravity stress This is associated with a high urinary output of norepinephrine On the other hand if they are anxious and worried about this stress they cannot tolerate a very high stress and their urine shows increased epinephrine This response can be modified depending on the circumstances Experimentally if we try to induce hypertension in animals we don t induce it in 100 per cent of the animals even with known hypertensive agents I think this in no way militates against the possibility of stress being one etiologic factor Dr Corcoran s remarks regarding the finding of normal renal function in patients with early essential hypertension are somewhat disturbing However like the levels of plasma ACTH or plasma 17 hydroxycorticoids during stress this has to be evaluated in the light of the patient s own control Often the values under stress are still within the normal range but yet significantly higher in response to this stimulus as compared with the patient s own control Finally the fact that we don t regularly demonstrate elevated catechol amine excretion also is not disturbing We study patients at a time when essential hypertension has become developed not when it is in its initiating phase The same statements could be applied to DCA hypertension in rats You remove the DCA after a certain length of time but the hypertension persists This doesn t rule out the fact that DCA has caused it It is possible that a combination of various pressor factors could be potentiating and yet still be within normal limits For example let s say circulating norepinephrine and mineralocorticoids were on the high normal side These values would be called normal but yet might potentiate each other and cause vasoconstriction

Part III

PHARMACOLOGY OF HYPERTENSION AND USE OF SYMPATHETIC BLOCKING AGENTS

General Considerations on the Pharmacology of Hypertension Therapeutic Aspects

JOHN H MOYER

Hahnemann Medical College and Hospital

Some of the previous papers have placed great emphasis on salt and water as the culprits and coconspirators in hypertensive disease I doubt that it is as simple as that It seems more likely that the patient with hypertension has a generalized disease and as Grollman has pointed out that many systems are involved There has been a tendency by numerous authors participating in this symposium to discount the importance of the central nervous and the autonomic nervous systems In studying the patient with established hypertension it seems to me that the nervous system is an integral part of the disease process If it is not a culprit then surely it is a victim

Some of the investigators who discount stress factors and altered nervous system activity as integral parts of the hypertensive process advocate home blood pressure recordings Why? Is it because the patient stops excreting salt and water when his blood pressure is taken in the doctors office or is it because of the patient s psychosomatic response to the doctor that causes the blood pressure to rise when the patient goes to the doctors office?

Although nervous system factors are difficult to measure and whether or not we like the idea all effective therapeutic programs which are in current use today include drugs which depress the activity of the sympathetic nervous system in one area or another Consequently we will spend much of our time for the next three days discussing the pharmacology of drugs which alter autonomic nervous system activity As a secondary consideration we will consider diuretics which augment the blood pressure responses to drugs which block sympathetic nervous system impulses most likely the diuretics produce this effect by increasing sodium excretion

In this presentation it should be made clear that the discussion revolves around the pharmacodynamics of established hypertension Etiologic implications should not be drawn since it is quite possible that the cardiovascular factors and dynamics which maintain the hypertensive state are entirely different from those forces which initiate the disease *de novo*

With the recent availability of compounds capable of blocking vasoconstrictor impulse formation and transmission of these impulses over the sympathetic nervous system rational and effective reduction of blood pressure in the patient with hypertension is possible The effectiveness with which the clinician is able to use these autonomic blocking agents depends to a large extent upon an understanding of the pharmacodynamics of autonomic drugs Beneficial results depend for the most part upon selecting the appropriate

drug for each given clinical situation and careful attention to such details as dose titration and follow up

There are many theories regarding the pathogenesis of hypertension For this presentation we prefer to think of increased vascular responsiveness to normal vasoconstrictor impulses or an increased number of impulses being discharged from the higher nervous centers such as the vasomotor centers as being responsible for maintaining the hypertensive state The end result is the same These impulses pass from the central nervous system over the sympathetic nervous system to sympathetic nerve endings at the arterioles thus initiating vasoconstriction which results in an increase in intra arterial

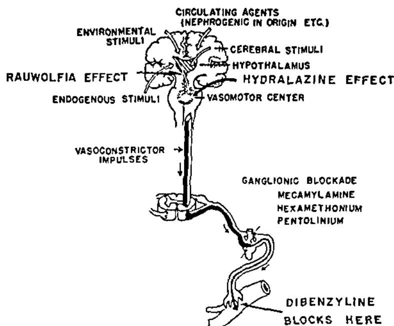


Fig 1 Diagrammatic presentation of the autonomic nervous system and the focal point of the maximum effect of different drugs which depress sympathetic nervous system activity as we know it today Nearly all of the drugs have effects other than the central nervous system effects particularly those which act centrally For example hydralazine appears to have some adrenergic blocking effect and Rauwolfia appears to deplete nor epinephrine at the neuroeffector site Nevertheless the diagram as presented here will serve for orientation of the discussion to follow

pressure Thus it would seem that blood pressure could be reduced by the suppression of these vasoconstrictor impulses at their sites of origin (central blockade) or blockade of the vasoconstrictor impulses along their transmission pathway either at the ganglion or at the sympathetic nerve ending (Fig 1) It is therefore obvious that since agents capable of acting on the autonomic nervous system are available they have become an important key to the treatment of clinical hypertension All of these agents however produce a variety of effects other than blood pressure reduction by virtue of their action on the nervous system Each of these so called side reactions is a predictable effect if the mechanism of action is understood A thorough understanding of these drugs will constitute the difference between success and failure of treatment

REVIEW OF THE PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system includes the sympathetic and parasympathetic nervous systems (see Fig 2) The sympathetic nervous system consists of central connections from which arise myelinated fibers which emerge from the spinal cord along with peripheral nerves They leave the spinal cord from the T 1 to the L 2 and 3 level (dorsal lumbar outflow) and

THE ROLE OF ACETYLCHOLINE EPINEPHRINE AND NOREPINEPHRINE IN THE AUTONOMIC NERVOUS SYSTEM

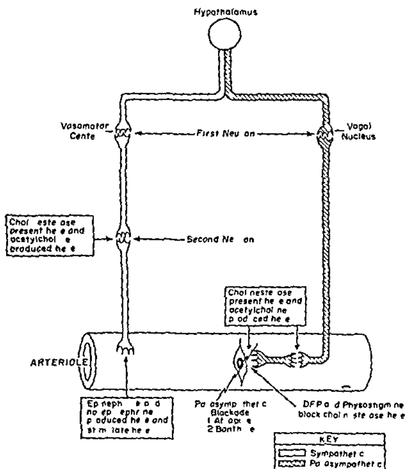


Fig 2 The place of acetylcholine in neurogenic transmission of impulses in the autonomic nervous system

terminate in sympathetic ganglia adjacent to or in contact with the post ganglionic neuron The greater lesser and least splanchnic nerves carry many such preganglionic neurons and are sectioned surgically when a "sympathectomy" is done The sympathetic ganglia of which the cervical celiac and mesenteric ganglia are examples are the site of synapse between the pre and postganglionic neurons The impulse is probably transmitted

across the synapse by the liberation of acetylcholine at the endings of the preganglionic fiber Cholinesterase is present in the tissues surrounding the synapse and quickly destroys acetylcholine after it has stimulated the post ganglionic neuron thus preventing its diffusion throughout the body In the blood vessels norepinephrine is the primary substance liberated after sym pathetic stimulation producing vasoconstriction and an increase in blood pressure

The basic pattern of the parasympathetic nervous system is similar to that of the sympathetic except that the preganglionic fiber runs directly from the central nervous system to the organ innervated to form a synapse with the postganglionic neuron within the organ The central connections are with the third seventh ninth and tenth cranial nerves and the sacral out flow tract Acetylcholine is liberated by the endings of the preganglionic fiber and stimulates the postganglionic neuron These in turn transmit the impulse a short distance to the effector site where again acetylcholine is liberated producing the characteristic effect (cholinergic response) upon the effector organ The acetylcholine liberated at these sites is quickly neu tralized by cholinesterase Pure parasympathetic effects (cholinergic re sponses) result in an increase in gastric motility and secretion bradycardia increase in bladder tone and relaxation of sphincter tone etc Other para sympathetic effects can be demonstrated in the laboratory but are not of importance in the current presentation

CLINICAL CONSIDERATIONS CONCERNING BLOOD PRESSURE REDUCTION

Most of the problems and complications of prolonged hypertension arise in three vascular beds the brain the heart and coronary vessels and the kidneys Also the benefits problems and complications arising from the treatment of hypertension are largely related to these three beds Each separate region will be discussed in reference to antihypertensive drug therapy

Cerebral function is definitely improved by lowering the blood pressure in hypertensive patients (Table 1) particularly if derangement of cerebral function secondary to the hypertension exists When blood pressure is re duced the cerebral vessels dilate and cerebral blood flow and metabolism are maintained (Fig 3 and Table 2) However if the blood pressure is reduced excessively cerebral blood flow decreases and disturbances in cere bral function follow resulting in symptoms of dizziness and syncope (Fig 4) This is particularly likely to occur in the upright position when some of the more potent peripherally acting drugs are used since reflexes responsible for adjusting peripheral vascular resistance to compensate for changes in position may be inhibited Therefore the blood pressure should always be taken both in the supine and upright positions when evaluating therapy An upright blood pressure of 150/100 mm Hg appears to be safe and allows for some fluctuation in blood pressure to occur I do not attempt to lower the supine blood pressure to absolute normotensive levels par ticularly when using an adrenergic blocking agent such as phenoxybenza mine (Dibenzyline) or a ganglionic blocking agent It is extremely impor tant that the dose of a ganglionic blocking agent be regulated according to the upright blood pressure Although cerebrovascular accidents have been

TABLE I BLOOD PRESSURE AND SYMPTOMATIC RESPONSE TO CONTINUOUS INFUSIONS OF INTRAVENOUS VERILOID FOR THE TREATMENT OF SEVERE ENCEPHALOPATHY

PATIENT	AGE	KNOWN DURATION (YRS)	DIAGNOSIS	PULSE RATE: CONTROL	PULSE RATE: DURING INFUSION OF VERILOID	BLOOD PRESSURE: CONTROL MEAN	BLOOD PRESSURE: DURING VERILOID INFUSION: MEAN	BLOOD PRESSURE: DURING VERILOID INFUSION: RANGE	SIDE REACTIONS	INFUSION PERIOD (HRS)	SYMPTOMATIC IMPROVEMENT (ENCEPHALOPATHY)
1	4[illegible]	10	CN*	77	50	210/140	158/104	180/120–130/80	None	72	++
2	21	8	HCVD†	66	44	260/150	155/90	170/100–130/72	None	49	++
3	38	7	HCVD	82	80	300/210	180/125	200/140–150/110	Weakness	96	+++
4	51	2	HCVD	100	60	290/160	140/120	160/130–130/108	Hiccough vomiting	24	+
5	[illegible]9	13	CN	107	109	234/162	160/110	198/140–110/80	Restless	48	+++
6	48	1	HCVD	120	100	230/164	150/90	160/108–138/80	Dizzy weak nausea	48	+++
7	52	10	HCVD	80	64	248/130	162/90	180/104–148/82	Dizzy	48	+++
8	33	6	CN	90	70	190/120	110/68	130/100–90/58	Vomiting	24	++
9	29	6	CN	80	64	220/160	130/95	150/108–110/90	None	18	Pt died
10	27	4	HCVD	104	70	265/170	155/105	170/115–130/100	Vomiting	72	+++
11	60	7	HCVD	84	70	235/150	170/110	190/120–135/90	Nausea	72	+++
12	55	0.5	CN	100	50	225/145	180/130	200/140–170/120	None	96	+
13	49	0.3	HCVD	72	58	310/220	240/160	260/180–200/130	Weakness hiccough	48	0
14	49	1	HCVD	84	76	[illegible]00/140	130/100	158/115–1[illegible]0/80	Vomiting	24	0
15	53	2	HCVD	80	66	190/125	130/110	170/120–110/98	Hiccough nausea	72	++
16	[illegible]6	1	HCVD	76	72	240/162	150/100	170/110–140/96	None	96	0
17	[illegible]4	1	HCVD	90	[illegible]6	300/210	158/110	200/130–110/90	Hiccough weakness	24	+++
Mean	44	4.7		88	69‡	243/159	156‡/107‡			55	

* CN = Chronic nephritis

† HCVD = Hypertensive cardiovascular disease

‡ Statistically significant change from control values ($p < 0.01$)

(From Moyer *et al* Am J Med *14* 175 1953)

TABLE 2 COMPARISON OF CEREBRAL HEMODYNAMIC RESPONSE TO ACUTE BLOOD PRESSURE REDUCTION WITH VARIOUS AGENTS IN HYPERTENSIVE AND NORMOTENSIVE SUBJECTS MEAN VALUES

TYPE OF PATIENT	DRUG ADMINISTERED	MEAN BLOOD PRESSURE mm Hg		CEREBRAL BLOOD FLOW cc /min		CEREBRAL OXYGEN CONSUMPTION cc /min		CEREBRO VASCULAR RESISTANCE		ARTERIAL P CO_2		NUMBER PATIENTS STUDIED
		C	D	C	D	C	D	C	D	C	D	
Severe Hypertensives	Phenoxybenzamine (Dibenzyline)	149	82	48	42	3 6	3 1	3 2	2 2	40	40	7
Severe Hypertensives	Alkavervir (Veriloid)	173	108	57	50	2 9	3 4	3 2	2 3	39	37	10
Severe Hypertensives	Dihydroergocornine	160	122	58	58	3 5	3 6	2 9	2 0	38	39	12
Normotensives	Hexamethonium	99	62	57	42	3 2	2 9	1 8	1 5	41	40	8
Normotensives	Dihydroergocornine	94	78	60	55	3 8	3 5	1 7	1 5	40	40	5

C = Control
D = After drug
(From Moyer *et al* Am J M Sc 228 563 1954)

reported with the use of these agents they are rare indeed Much more frequent is a cerebral hemorrhage resulting from a sudden rise in blood pressure It is believed that blood pressure reduction offers protection against cerebral hemorrhage and if the foregoing precautions are adhered to danger of thrombosis is minimal An additional gratifying effect of therapy is the marked relief of hypertensive headaches and encephalopathy (Table 1)

In regard to cardiac considerations improvement in anginal syndromes seen in many instances suggests that the ratio of coronary blood flow to oxygen and metabolite demand is improved Apparently reduction in work load on the heart (by reducing blood pressure) compensates for any de

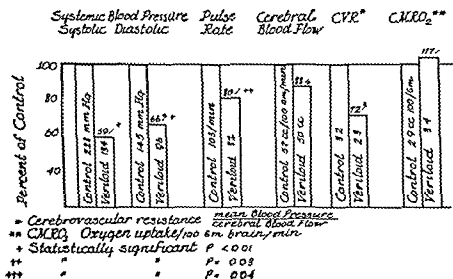


Fig 3 Cerebral hemodynamic response to blood pressure reduction with the Veratrum preparation alkavervir in a group of patients who had severe hypertensive vascular disease As the blood pressure was reduced there was a reduction in cerebral vascular resistance so that cerebral blood flow was not altered to a significant extent (From Am J Med 14 175 1953)

crease in coronary blood flow which might occur It is quite possible that with ganglionic blocking agents vasoconstrictor impulses travelling to the coronary arteries are blocked Also with ganglionic blockade of cardio-accelerator nerves the pulse rate is not increased The validity of the conclusion that the coronary circulation is not seriously impaired, particularly with ganglionic blockade is borne out by the observation that it is rare to see coronary thrombosis despite occasional excessive hypotensive episodes On the contrary the cardio-accelerator effect of hydralazine when used as the only medication may have dangerous potentialities in patients with coronary artery disease and is frequently associated with angina tachycardia, palpitation and occasionally myocardial infarction Generally cardiac failure is improved following blood pressure reduction When the blood

pressure is reduced with hexamethonium in patients with heart failure there is an increase in cardiac output and lowering of the right ventricular and pulmonary arterial pressures which is followed by improvement in cardiac failure

If pretreatment renal function is not impaired renal vascular resistance decreases and renal blood flow is not altered significantly with blood pressure reduction by autonomic blockade If impairment of renal function is marked caution must be exercised when reducing the blood pressure to avoid impairment of renal excretory capacity Following acute blood pressure reduction there is an initial depression of renal function However glomerular filtration rate gradually returns to normal despite a maintained

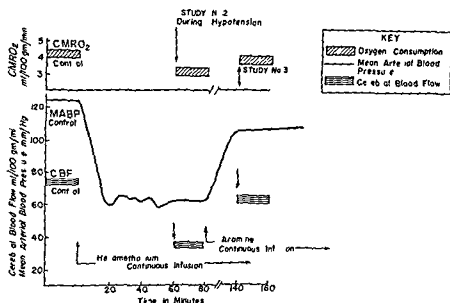


Fig 4 Although the cerebral blood flow is not altered significantly with mild to moderate reductions in blood pressure when the blood pressure is reduced to hypotensive levels in patients with hypertension there is a significant reduction in cerebral blood flow When blood pressure reduction is excessive the oxygen taken up by the brain (CMRO) is also depressed These responses can be reversed by the infusion of any vasopressor agent which is effective in elevating the blood pressure (From J Clin Invest 33 1081 1954)

reduction in blood pressure provided the reduction is not excessive Patients with renal damage respond qualitatively similarly to patients with normal kidneys but the readjustment is slower and occasionally incomplete If readjustment is incomplete and if renal function is markedly impaired even small reductions in glomerular filtration rate may be serious enough to decompensate the kidney and cause frank renal failure Incomplete renal hemodynamic readjustment is more likely to occur if the blood pressure is reduced to absolute normotensive or hypotensive levels This does not indicate that blood pressure reduction is not desirable in the presence of impaired renal function It does indicate that when blood pressure reduction is undertaken it must be done with extreme caution maintaining the standing blood pressure somewhat above normotensive levels Constant awareness of renal excretory function is necessary and any tendency toward

an increase in the blood urea nitrogen is a definite contraindication to greater reduction in blood pressure If the blood urea nitrogen cannot be determined repeatedly hypotensive therapy should not be undertaken in patients exhibiting azotemia It is important to realize that the blood pressure can be reduced in patients exhibiting hypertension secondary to renal disease equally well as in patients with essential hypertension

AUTONOMIC BLOCKING AGENTS WHICH HAVE A PRIMARY CENTRAL EFFECT

The central agents of which Veratrum hydralazine and Rauwolfia are the most important block or suppress vasoconstrictor impulses in the central nervous system at the hypothalamus and/or vasoregulatory (vasomotor) centers These agents also have peripheral action which will no doubt be emphasized by the other symposium participants speaking on this subject These agents do not significantly block the reflexes which occur with changes in posture so that the blood pressure reduction achieved by them is present in all positions not just in the erect position In general they exert only a mild to moderate effect on the blood pressure when given orally Excessive hypotension after either the oral or parenteral route may be rapidly combated with norepinephrine or any other effective vasopressor agent Each of these hypotensive agents has unpleasant side effects which will be described in greater detail by other authors Veratrum derivatives particularly stimulate the emetic center so that vomiting commonly occurs when a therapeutic dose is reached More purified preparations have been introduced recently to obviate this response but vomiting continues to be a common problem with Veratrum therapy Chlorpromazine (Thorazine) has been used with Veratrum without significantly lessening the incidence of vomiting

GANGLIONIC BLOCKING AGENTS

These compounds are among the most potent agents that can be given by mouth The quaternary ammonium compounds hexamethonium tetraethylammonium and pentolinium are absorbed rather poorly from the gastrointestinal tract so that regulation of oral therapy is somewhat difficult Mecamylamine on the other hand is readily and completely absorbed from the gastrointestinal tract rendering it more effective All ganglionic blocking agents interfere with reflexes responsible for adjusting the blood pressure to postural change Therefore these agents reduce the erect blood pressure more than the supine blood pressure All produce a parasympathetic as well as sympathetic blockade Therefore constipation urinary difficulties and dryness of the mouth are common complaints in addition to postural dizziness and syncope Excessive hypotension may be combated with norepinephrine or any other pressor agent

ADRENERGIC BLOCKING AGENTS

Adrenergic blocking agents block the transmission of impulses from the postganglionic ending to the effector site The adrenergic blocking agents in low concentration produce a humoral blockade of circulating epinephrine and norepinephrine Because of this fact they are useful in low dosage as a diagnostic test for pheochromocytomata In larger dosage they produce a

true adrenergic blockade at the neuro effector site in addition to the blockade of circulating norepinephrine With adrenergic blockade as with ganglionic blockade the blood pressure reduction is primarily postural In addition to this these compounds block norepinephrine or any other pressor agent which might be given to combat excessive hypotension With the exception of Dibenzyline the adrenergic blocking agents which include Regitine Benzodioxane and Dibenamine are not dependable when given by mouth An additional difficulty is that tolerance to the drugs develops quickly Therefore they are not effective when used for the treatment of clinical hypertension *The chief use of Benzodioxane and Regitine is as a diagnostic* test for pheochromocytomata

Dibenzyline has been used both alone and in combination with Rauwolfia the latter being a potent hypotensive combination

COMBINATION DRUG THERAPY

The over all picture of autonomic blocking agents suggests that virtually all have undesirable effects as well as some advantages In general the more potent the agent the more difficult it is to administer It has been postulated therefore that by giving two or more agents concomitantly one might achieve an additive hypotensive effect and at the same time a reduction of the undesirable side effects which are noted when any one of the drugs is used alone There are several notable examples of this Hexamethonium pentolinium or Rauwolfia will block the cardio accelerator effect by hydralazine Rauwolfia when used in combination with ganglionic or adrenergic blocking agents will permit a lower dosage of the more potent agents to be used and thus some of the untoward effects of ganglionic or adrenergic blocking agents may be reduced At this writing, experience suggests to me that a natriuretic agent such as chlorothiazide (or hydrochlorothiazide) should form the background or base medication for the initiation of treatment of all degrees of hypertension to which the autonomic blocking agents are added as necessary Probably Rauwolfia should be given an initial trial with chlorothiazide in all patients Patients with mild or labile hypertension will sometimes become normotensive on this combination alone If the response is suboptimal a more potent antihypertensive agent may be added to the Rauwolfia and chlorothiazide With severe or rapidly progressive hypertension chlorothiazide and Rauwolfia plus a more potent agent should be started together from the outset of therapy

DIURETICS

The importance of salt and water metabolism in patients with hypertension should not be underestimated Although it is generally agreed that the total body sodium content is not increased in patients with essential hypertension and that the body turnover of salt is not increased when people take a very high salt diet hypertension is seen more frequently than in a population where the salt intake is low As has been shown by Dr Meneely and others in this symposium the blood pressure can be increased in rats with a high sodium intake The process can be hastened by the administration of DCA At the same time it appears that potassium counteracts this response to a significant degree

Clinically it is evident that a high salt intake aggravates the hypertensive state after the disease has been established In addition Kempner Grollman Corcoran and many others have shown that when the intake of sodium is adequately low there is a tendency toward blood pressure reduction and reversal of the hypertensive symptoms However this is not a very effective approach to treatment of hypertension, since the diet is unpalatable and the response is not adequately consistent. This has led to the use of drugs which enhance sodium excretion Thus rather than severely reducing the intake diuretics can be given which increase the sodium output at the same time that the diet remains palatable In order for the diuretics to be most effective it is important that some measure of control of sodium intake be undertaken It is usually a good idea to attempt to keep the sodium chloride content in the diet at about 3 gm per day This is a palatable diet and at the same time the intake of sodium can be kept rather constant

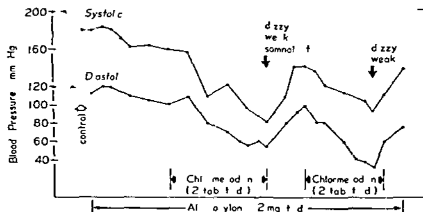


Fig 5 Blood pressure response to the diuretic chlormerodrin (Neohydrin) given to a patient who was already receiving Rauwolfia. The blood pressure response was rather marked. When the diuretic was withdrawn the hypotensive effect that was observed after the administration of the diuretic was lost. This response could be repeated

Because of the side effects associated with diuretics which may be administered orally this has not been a very popular therapy until recently None theless diuretics such as chlormerodrin (Neohydrin) have been quite effective in enhancing the hypotensive response to drugs which depress the sympathetic nervous system For example in Figure 5 is summarized the treatment of a patient who was given Rauwolfia with an inadequate response When the diuretic chlormerodrin (Neohydrin) was added there was a significant reduction in blood pressure When the chlormerodrin was discontinued the blood pressure rose again When it was reinstituted there was again a reduction in blood pressure This indicates that the natriuretic agent in this instance enhanced the hypotensive response to Rauwolfia This is not a new observation since this study was done in 1953

More recently a group of drugs has been developed which are more

potent than chlormerodrin in addition the incidence of side effects is much less particularly the incidence of nausea and vomiting These new agents belong to the thiazide group of drugs of which chlorothiazide was the first to be developed These compounds are quite effective when given orally and when administered by this route are as potent as meralluride (Mercuhydrin) given daily by the parenteral route The primary effect of chlorothiazide is on sodium and chloride excretion The pharmacology of this compound will be described in detail by various authors in this conference Hydrochlorothiazide which is more potent than chlorothiazide and flumethazide will also be described by other participants in this conference The virtue of flumethazide is that it has less effect on potassium excretion than chlorothiazide The virtue of hydrochlorothiazide is that it is more potent than chlorothiazide At the same time it seems to produce a greater increase in potassium excretion Certainly its effect on chloride excretion is more marked so that the chloride excretion is considerably greater than sodium excretion sometimes leading to hypochloremic alkalosis

Chlorothiazide has been studied as the sole therapeutic agent in hypertensive patients In severe hypertension (or even in moderately severe hypertension) it has not been very effective when given alone The chief virtue of chlorothiazide is the potentiating effect that it exerts on drugs which depress the autonomic nervous system Figure 6 summarizes the treatment of a patient who had a minimal response to a combination of the ganglionic blocking agent mecamylamine and reserpine When chlorothiazide was given there was a marked enhancement of the hypotensive effect even at half the dose of the ganglionic blocking agent However note that the primary effect was that of enhanced ganglionic blockade since the orthostatic response was much greater than the supine response This enhancing effect is lost quite rapidly when the drug is discontinued as seen in Figure 6

Accompanying the enhancing effect of the autonomic drugs by chlorothiazide is a persistent increase in sodium excretion associated with weight loss Freis and his associates have demonstrated that this is due to a reduction in extracellular fluid volume as well as in plasma volume The effect on sodium excretion and weight loss is seen in Figure 7 which concerns the same patient whose blood pressure response is recorded in Figure 6 After prolonged administration of chlorothiazide equilibration finally results so that the output of sodium approximates the intake

It is my belief that the blood pressure effect cannot be explained solely as a reduction of blood volume it is not quite apparent to me why the vascular system could not compensate for a 10 to 15 per cent reduction in blood volume In addition there is a marked enhancement of the other effects of autonomic drugs For example the parasympathetic effects of ganglionic blockade are all enhanced when chlorothiazide is given with the blocking agent including the eye signs the constipation and the dry mouth which are untoward parasympathetic effects

Freis and his associates have shown that the depressor response to ganglionic blockade (Arfonad) is enhanced in patients who have received chlorothiazide In addition the pressor response to vasopressor agents such as norepinephrine is reduced Indeed this can be confirmed (Fig 8) However I am not at all sure that this is not due to a reduction in effector site responsiveness of the smooth muscles of the arterioles to norepinephrine

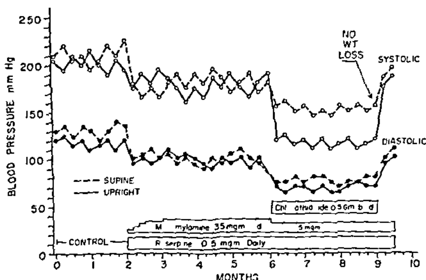


Fig 6 Blood pressure response wl en chlorothiazide was given in a dose of 0 5 gm twice a day to a patient who was already receiving a ganglionic blocking agent and Rauwolfia There was a marked enhancement of tl e hypotensive effect which was largely orthostatic in nature typical of the ganglionic blockade (From Ann New York Acad Sc 71 456 1958)

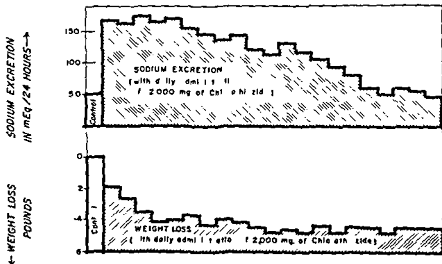


Fig ⁻ The effect of cl lorotl iazide on sodium excretion and w eigl t loss during tl e period of d uretic admini tration to the same patient (Fig 6) at the time that the maxi mum effect on blood pres ure was ol erved At the same time that tl ere was a marked enhancement of l lood pressure reduction sodi im excretion was increased. This was associated with wei ht l s apparently due to a reduction in extracellular fl uid. Whether tl e blood pressure effect was due to reduced extracell ilar fluid and subsequent reducti n in blood volume or whether it was due to altered concentration of sodium in certain tissues of the body has not been clearly established as yet

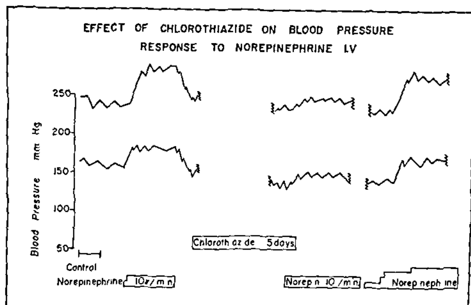


Fig 8 Blood pressure response to norepinephrine before and after the administration of chlorothiazide The patient was much less responsive to a similar dose of norepinephrine following natriuresis

which is also the recognized chemical mediator of sympathetic vasoconstrictor impulses It might well be that mobilization of tissue sodium as a direct result of the natriuretic effect of chlorothiazide is responsible for this response rather than the reduction in blood volume

One reason for having some doubts that reduction in blood volume is the sole factor responsible for enhancement of the blood pressure response to ganglionic blocking agents by chlorothiazide is that similar responses are seen when ganglionic blocking agents are given in the absence of diuretic agents such as chlorothiazide and in the absence of reduced blood volume For example when hexamethonium was infused into normotensive subjects there was an increase in plasma volume of about 17 per cent associated with a reduction in blood pressure (Table 3) When small amounts of blood were withdrawn in amounts of 25 to 50 cc there was a sharp additional reduction in blood pressure under these circumstances After a period of time the blood pressure gradually returned toward the previous level or

TABLE 3 EFFECT OF HEXAMETHONIUM ON BLOOD VOLUME WHEN GIVEN BY CONTINUOUS INFUSION FOLLOWED BY THE WITHDRAWAL OF SMALL AMOUNTS OF BLOOD (16 PATIENTS)

	ARTERIAL BLOOD PRESSURE (mean mm Hg)	BLOOD VOLUME (cc)	PLASMA VOLUME (cc)	RED CELL MASS (cc)
Control	103	5407	3177	2230
Hexamethonium	65	6083*	3722	2360
Blood Withdrawal (50 cc)	51	6033†	Not Determined	

* 112% of control
† 111% of control

if the blood was replaced there was a more rapid increase in blood pressure to the control (postblocked) blood pressure Consequently the blood volume was never reduced below the control value in these patients and yet the same type of response was seen that Dr Freis has observed when withdrawing blood from patients given chlorothiazide and ganglionic blocking agents concurrently Reduced blood volume is probably an important factor in the mechanism of the response to chlorothiazide but I doubt that the cause and effect relationship is as simple as a decrease in blood volume only

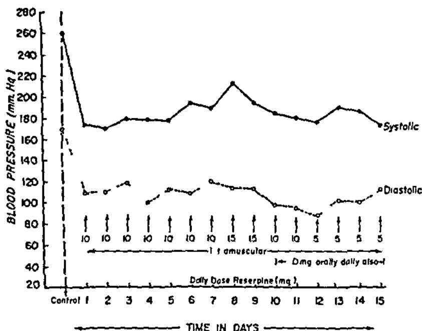


Fig 9 Blood pressure response to reserpine given parenterally in a patient with severe essential hypertensive cardiovascular disease There was a significant reduction in blood pressure (From A M A Arch Int Med 95 563 1955)

THE NONSPECIFICITY OF BLOOD PRESSURE RESPONSE IN PATIENTS WITH ESSENTIAL HYPERTENSION AS COMPARED TO HYPERTENSION ASSOCIATED WITH OTHER DISEASE ENTITIES

In past communications I have frequently attempted to point out the common denominator of sympathetic vascular reactivity in hypertension due to numerous causes These observations have been largely based on pharmacologic evidence The observations in actuality have no etiologic significance and are of importance in the already established hypertensive syndrome only

Reserpine Irrespective of the cause of hypertension the blood pressure response to drugs which depress the sympathetic nervous system given alone and in combination with diuretics is quite striking For example in Figure 9 is seen the typical blood pressure response to reserpine in a patient

Reserpine 5 Mg IV

Reserpine 5 Mg IM

Hydralazine 10 Mg IV

Delivery

220 200 180 160 140 120 100 80 60 40 20 0

15 30 45 15 30 45 15 30 45

B P Readings Taken Every 15 Minutes

Fig 10 Blood pressure response to reserpine and hydralazine in a patient with severe preeclampsia and hypertension The blood pressure response could be repeated with repeated doses of reserpine The reduction was more effective after the administration of hydralazine

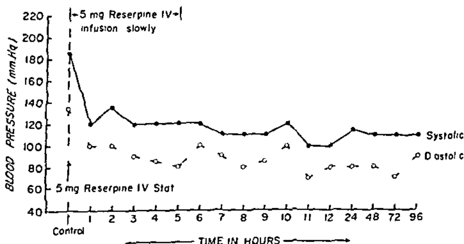


Fig 11 Blood pressure response in a patient with hypertension associated with preeclampsia when given 5 mg of reserpine parenterally (From A M.A Arch Int Med 95 563 1955)

Fig 12 Blood pressure response in a patient with hypertension associated with acute nephritis There was no doubt that the drug was effective in lowering the blood pressure

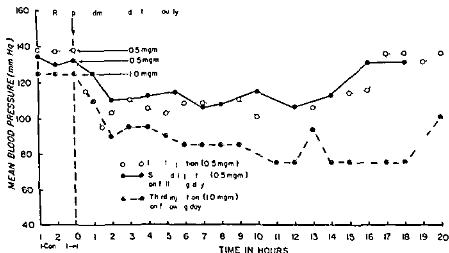


Fig 13 Responses to reserpine administered repeatedly in a child with acute glomerular nephritis There was a significant reduction in blood pressure each time that the drug was given (From A M A Arch Int Med 95 563 1955)

with severe hypertensive cardiovascular disease of the essential variety A similar response is seen in the patients summarized in Figures 10 and 11 with severe preeclampsia Both of these patients had a significant response to reserpine given intravenously An even greater response was seen when hydralazine was given to the patient in Figure 10 In Figures 12 and 13

are seen the responses in two children with hypertension who had elevated blood pressure in association with acute glomerular nephritis The blood pressure response here was quite significant and quite similar to that observed in a patient with severe essential hypertension

Of even more significance is the response seen in a patient with occlusion of one renal artery—the counterpart of the Goldblatt preparation in the dog The patient illustrated in Figure 14 had a severe hypertension following occlusion of the right renal artery When reserpine was given there was a significant reduction in blood pressure It seems quite likely to me that if the hypertension had been due to a vasoconstrictor substance acting directly on the muscle of the arterioles and distal to the neuroeffector transmission site the blood pressure would not have responded in this fashion

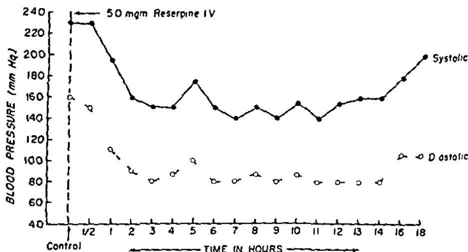


Fig 14 Blood pressure response to reserpine in a patient who had occlusion of the right renal artery The reduction in blood pressure was equally marked as it is in patients with essential hypertension This would lead one to the conclusion that the factors responsible for maintaining the blood pressure in this patient are not essentially different from those present in patients with essential hypertension acute glomerular nephritis or toxemia of pregnancy One common denominator in hypertensive vascular disease which is already established appears to be the sympathetic nervous system (From Am J Med 24 177 1958)

whether reserpine acts centrally in the brain or through the sympathetic nerve ending by depleting norepinephrine in this area In fact when norepinephrine was infused parenterally into this patient at the time that his blood pressure was reduced he was quite responsive to this compound in that his blood pressure was elevated rather easily In fact he had a greater response in blood pressure following the administration of reserpine than was observed at the time that his blood pressure was elevated Consequently it is difficult to see how anything other than depression of the sympathetic nervous system was responsible for the reduction in blood pressure in this case It is even more difficult to see how anything other than increased sympathetic vascular reactivity was responsible for maintaining the blood pressure prior to the administration of reserpine if reserpine acts by either depressing the sympathetic nervous system or depleting norepinephrine at the neuroeffector site

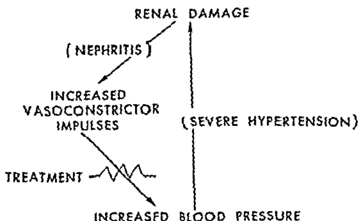


Fig 15 A diagrammatic representation of the interrelationship of essential hypertension and hypertension associated with primary renal disease It would appear that the increased blood pressure produces increased renal vascular damage irrespective of whether primary renal disease is present or not At the same time it appears that primary renal disease is associated with abnormal function of the autonomic nervous system at least after the process has been established It appears that effective blockade of transmission of impulses over the autonomic nervous system arrests this vicious cycle Consequently treatment is effective whether the primary process originates in the kidney or whether it originates elsewhere as in essential hypertensive disease of unknown etiology

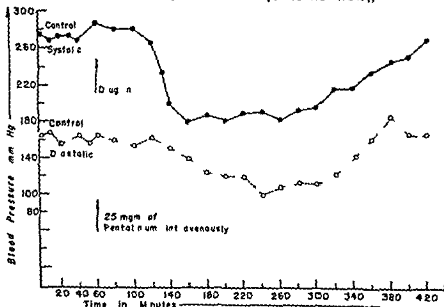


Fig 16 The effect of intravenously administered pentolinium in a patient with renal artery occlusion Although the reduction in blood pressure is not nearly as marked as in a patient who has received reserpine there is a definite effect on the blood pressure here much as is seen in the patient with essential hypertension

As Dr Grollman has pointed out on several occasions in this symposium essential hypertension is probably a multisystem disease after it is established One of the systems involved is the nervous system Consequently it seems to me that abnormality of the autonomic nervous system is at least one common denominator in the hypertensive syndrome even though it may not be important etiologically It would appear that even in the patient with definite renal involvement there is a nervous system component (Figs 12 13 and 14) Thus when renal disease exists it seems likely that

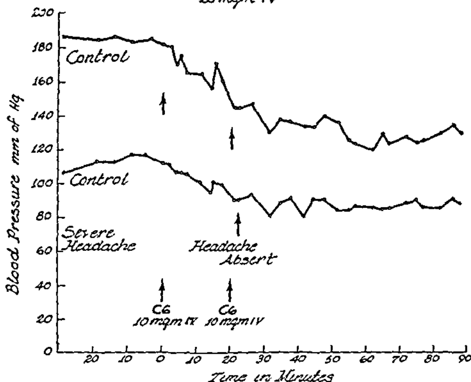


Fig 17 Response in a patient with essential hypertension to ganglionic blockade There is very little difference in response here as compared to the previous patient (Fig 16) who had hypertension of renal origin due to occlusion of the renal artery

in some way probably humoral the effect of the damaged kidney is transmitted through the central nervous system which in turn produces abnormality of function (Fig 15) in the autonomic nervous system

Ganglionic Blocking Agents It is recognized that ganglionic blocking agents do not produce a potent reduction in blood pressure in most patients with hypertension irrespective of the etiology when the patient is in the supine position probably because of incomplete blockade of the sympathetic nervous system as pointed out on several occasions here by Dr Paton Nonetheless the response to hypertension of renal origin is no less than the response in patients with so-called essential hypertension Two such cases are presented in Figures 16 and 17

The Pharmacology of Rauwolfia Compounds (including Syrosingopine)

ALBERT J PLUMMER

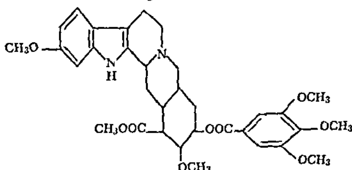
Research Department CIBA Pharmaceutical Products Inc

The Rauwolfia plant a member of the genus Aponyaceae is indigenous to the subtropical zones of Asia Africa and South America In the various areas in which it grows the natives of the region have employed the roots of the plant for treating a variety of illnesses The species has been named in honor of Leonhard Rauwolf of Augsburg a physician who traveled to India in 1582 in search of plants of medicinal interest Although the use of *Rauwolfia serpentina* so named because of the snakelike appearance of the root, goes back in native Indian medicine to most ancient times it is only within the past decade that the plant has gained a place in modern therapy In accounts of the early use of Rauwolfia in India its sedative component was most prominently mentioned as being beneficial in the treatment of excited and disturbed individuals Chopra [1] in 1933 provided the first pharmacologic basis for such an action when he observed a sleepy state in experimental animals following the administration of crude Rauwolfia extracts

The hypotensive effect of Rauwolfia which is characteristically subtle escaped detection until Chopra and his co workers in 1942 obtained a hypotensive response with a total extract of *Rauwolfia serpentina* in animals in which an experimental hypertension had previously been induced Seven years later in 1949 Vakil[3] reported the therapeutic value of *Rauwolfia serpentina* in human hypertension On the basis of Vakil s report Wilkins[4] carried out clinical trials in this country also with favorable results

A systematic study of the alkaloids of *Rauwolfia serpentina* had already been made by Siddiqui and Siddiqui[5] as early as 1931 but none of the various substances isolated including ajmaline and serpentine had shown the sedative or hypotensive activity characteristic of the whole root Gupta and his associates [6] in 1944 prepared an extract of *Rauwolfia serpentina* free of all the known alkaloids but exhibiting the sedative action of gradual onset and long duration peculiar to the total extract of the plant The ultimate isolation of the substance responsible for the sedative action noted by Gupta was achieved in 1952 by Mueller Schlittler and Bein [7] who identified it as a tertiary indole alkaloid Subsequently Bein[8] demonstrated that this substance which was given the generic name reserpine also exerted a hypotensive action in experimental animals which like the quieting action was also slow in onset but persistent in its effect

The chemical structure of reserpine the trimethoxybenzoate ester of methyl reserpate is the following



It was first demonstrated by Bein and confirmed by Plummer *et al*[9] that reserpine was responsible for the characteristic hypotension and sedation produced by the oral administration of Rauwolfia root Two alkaloids subsequently obtained from Rauwolfia root have also shown this typical reserpine-like activity These are rescinnamine identified by Klohs[10] and deserpidine identified by Schlittler *et al*[11] Rescinnamine is the trimethoxycinnamate of methyl reserpate and deserpidine differs from reserpine by the absence of the methoxy group on Ring A From a pharmacologic standpoint the general actions of reserpine are also manifested by both deserpidine and rescinnamine the latter substance having a potency of about half that of reserpine Of the many other Rauwolfia alkaloids extracted from various species none have exhibited the progressively developing central nervous and circulatory effects of reserpine In our experience the rapidly developing hypotensive effect of acute onset produced by the intravenous administration of Rauwolfia extracts free of reserpine are not obtainable upon oral administration to a conscious animal and hence would not appear to be available therapeutically when given *per os* Recent comprehensive reviews by Bein[12] and by Schneider[13] discuss in detail the pharmacology of these other alkaloids including ajmaline serpentine serpentenine and others Since the important pharmacologic actions of Rauwolfia are embodied in reserpine it will be convenient to use this substance as a prototype in the balance of this discussion

GENERAL EFFECTS ON BEHAVIOR AND APPEARANCE

When administered to a normal animal the most obvious effect of reserpine is the production of a quiet sedated state as first reported by Bein[8] for the rabbit This effect has been noted without exception in all species studied including the dog cat, rat mouse guinea pig, and monkey In such a state a dog which previously has shown great interest in his surroundings now becomes less concerned with the activity about him and lies quietly unless disturbed In some cases a period of hyperactivity and accelerated respiration may precede the state of quietude Eventually the respiratory rate becomes slowed when the animal has been sedated The monkey normally a wary animal characteristically becomes less apprehensive and may be approached handled and even stroked with comparative safety The rate of onset and the duration and intensity of these effects depend upon the dose and route of administration[9] However a true hypnotic state is not achieved since animals may be readily aroused after large doses of reser

pine There is also a marked difference in species sensitivity to reserpine For example an adequate single intravenous dose for quieting a dog is about 0 1 mg /kg while the monkey requires about 2 0 mg /kg for a comparable effect With these doses onset of activity may be seen in about an hour On a chronic basis the dog may be kept in a steady tranquil state on a maintenance dosage of 15 to 20 mcg /kg orally each day Animals have been so maintained for periods up to two years without any evidence of toxic side effects

The decrease in spontaneous activity which is associated with the tranquilizing effect of reserpine may be measured objectively in an activity recording apparatus or jiggle cage In a sensitive apparatus prepared for this purpose by Anderson[14] the activity of mice is markedly decreased after a latent period of about two hours by a dose of 2 5 mg / kg of reserpine subcutaneously

Reserpine also has the capacity to modify the behavioral expression of emotion or anxiety in conditioned rats in a test situation elaborated by Brady[15] Food deprived rats are trained to press a lever in a test chamber in order to obtain a ration of food At intervals a clicker is sounded for three minutes and a brief painful shock is administered to the animal through the grid floor of the cage simultaneously with the termination of the sound During the clicker period the conditioned rat ceases to press the lever and presents an appearance of fear and apprehension characterized by crouching trembling piloerection urination and defecation The behavior of the rats in this stressful situation is modified by rather low doses of reserpine For example a single intraperitoneal injection of 0 025 mg /kg largely eliminates the fear pattern induced by the clicker and restores the reduced rate of lever pressing to normal This dose of reserpine has no effect on the activity or appearance of the rats as judged by careful observation of the animals thus indicating that subtle effects on affective behavior due to an action upon the central nervous system may be achieved with minute amounts of reserpine

CARDIOVASCULAR ACTIONS

The hypotensive effect of reserpine can be obtained in the normotensive rabbit cat or dog under Dial Urethane or Nembutal anesthesia A dose of 0 1 mg /kg is sufficient in the rabbit while 0 3 to 0 5 mg /kg is required for the dog The fall in mean arterial blood pressure in anesthetized animals averages 25 to 35 mm Hg and develops gradually reaching a maximum over a period of three to four hours Accompanying the hypotensive response there is a gradual abolition of the reflex pressor response following carotid occlusion or central vagal stimulation together with a bradycardia and augmentation of the pressor response caused by the injection of epinephrine

In unanesthetized normotensive dogs the daily oral administration of 50 mcg /kg causes an average drop in mean arterial blood pressure of 25 mm Hg and of ten beats per minute in the heart rate after seven to ten days There is a return to normal blood pressure and heart rate over a period of seven days following cessation of reserpine treatment Neurogenic hypertensive dogs prepared by the ablation of both carotid sinuses the section of the left vago-sympathetic trunk and of the medial third of the right vagal trunk, are more susceptible to the cardiovascular actions of reserpine The elevated blood pressure in this case after a latent period of several days is

lowered 50 or 60 mm Hg by 10 to 20 mcg /kg of reserpine orally each day In addition the lability of the pulse rate with resulting pressor spike associated with even mild excitement in the neurogenic hypertensive animal is practically eliminated The blood pressure of the unanesthetized dogs *in these tests was obtained by femoral punctures in animals which had* been trained to accept this procedure quietly and without excitement

The bradycardia which reserpine produces in the intact dog does not occur in the Starling heart lung preparation As a matter of fact a tachycardia is caused in this preparation when 0 01 to 0 02 mg /ml of reserpine is added to the blood perfusing the heart Concurrently with the onset of bradycardia in the cat Bein[16] has noted a marked decrease in the nerve action potentials recorded from the cardio accelerator nerves Since there was no evidence that reserpine caused ganglionic blockade or adrenolytic activity with the doses employed these results suggested a reduction in sympathetic activity at a point central to the ganglia

No significant reduction in the cardiac output accompanies the hypotensive action of reserpine in the dog [17] but rather a decrease in peripheral resistance appears to be responsible for the fall in blood pressure

Reserpine has an ameliorating effect on the hypertension induced in rats by injection of desoxycorticosterone or cortisone[18, 19] and also hinders to a considerable degree development of adrenal regeneration hypertension in the rat [20]

OTHER ACTIONS OF RESERPINE

Miosis is the first effect of reserpine to appear and the last to disappear in the dog monkey and other species studied A single oral dose of 50 mcg /kg suffices to cause pupillary narrowing in the dog Shortly thereafter relaxation of the nictitating membrane is apparent in animals possessing this structure Ptosis of the upper eyelid also is evident These effects may be obtained in doses too small to cause obvious sedation and the miosis especially may last for several days after even a small dose In the unanesthetized dog excitement or the intravenous administration of a few mcg /kg of epinephrine causes a transient constriction of the relaxed nictitating membrane indicating *that the smooth muscle of the structure is capable* of responding properly

Hypothermia has been noted in the monkey following reserpine [1] the extent of the fall in body temperature being related to the reserpine administered The hypothermia develops in an environment temperature of 74 degrees F but not at 89 degrees F suggesting a diminution but not a suspension of the function of the heat regulatory mechanism

Reserpine has a general stimulatory action upon both the motor and secretory functions of the gastrointestinal tract The dog lends itself particularly well to this type of study since it is possible to use chronic preparations with gastric fistulae or with Pavlov or Heidenhain pouches Increased gastric acid secretion may be obtained by doses as low as 15 mcg /kg in the anesthetized dog In the unesthetized dog reserpine intravenously increases the tone and activity of the small intestine or the colon Since these motor and secretory effects are somewhat reduced but still obtainable when the vagi have been cut and the *spinal cord transected at C6* it appears that a peripheral action of reserpine is at least partially responsible for these actions [2]

DISCUSSION

The interesting and widespread influence which reserpine exerted on a variety of bodily systems has led to considerable study designed to explain its mechanism of action This has proved to be a complex problem however and much remains to be settled By the same token much has been accomplished as well and it will be appropriate to trace this progress

It was early noted that many of the actions of reserpine could be related to an alteration of the balance existing between the two divisions of the autonomic nervous system Because the nictitating membrane obtains its motor supply solely from the sympathetic nervous system it appeared that its relaxation must be related to reduced activity of this innervation Since the membrane was responsive to epinephrine and also since ganglionic blockade and adrenergic blockade were not produced by amounts of reserpine relaxing the membrane it appeared that its action upon the sympathetic nervous system was exerted at a higher level presumably within the central nervous system

Several other actions of reserpine may logically be ascribed to reduced sympathetic nervous tone These include (1) miosis (2) hypotension (3) reduced peripheral resistance (4) decreased pressor reflex reactivity (5) hypothermia (6) bradycardia (7) ptosis and (8) increased motor and secretory activity of the gastrointestinal tract In the face of this evidence the hypothesis was developed that reserpine depressed the activity of the sympathetic centers in the hypothalamus The sedative effect of reserpine would be consistent with such a concept since Hess [3] has provided evidence that sleep is a parasympathetically mediated function brought about by a suspension of the activity of the sympathetic center in the hypothalamus A substance such as reserpine by causing a partial suspension of the activity of the sympathetic center in the hypothalamus might well favor a state of quietude It is an established physiologic concept that emotional reactions are mediated through hypothalamic centers and that these may in turn be controlled or dampened by cortical activity By analogy the reduced emotional reactivity in the reserpinized Rhesus monkey may be ascribed to hypothalamic inhibition mediated pharmacologically Any such action by reserpine does not appear to be a direct one however for Schneider [4] was able to show that the pressor effect due to direct electrical stimulation of the hypothalamic sympathetic region was unaltered by definitely quieting doses of reserpine in the cat Additional support for an indirect inhibitory action of reserpine was provided by Bein [16] who demonstrated that the carotid occlusion pressor response which had been suppressed by reserpine returned upon a brain transection interrupting the corticothalamic pathways

The observations just described suggested that reserpine was acting by stimulating areas which in turn exerted an inhibitory influence over the hypothalamus through nervous connections In fact evidence has been obtained that reserpine is capable of stimulating certain functions of the brain For example Chen has found that the threshold for electroconvulsive shock and for Metrazol induced convulsions is lowered by reserpine In addition Rinaldi and Himwich [8] have shown that reserpine has an alerting effect by stimulation of the activating reticular system arousal mechanism Moreover Killam [7] has shown that spontaneous seizures have been produced by reserpine in the amygdala region of the rhinencephalon Such

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Mechanism of Hypotensive Action of Therapeutically Useful Veratrum Alkaloids

BENEDICT E ABREU

Research Center Pitman Moore Company and Indiana University School of Medicine

The general pharmacology of Veratrum alkaloids has been adequately reviewed by Krayer and Acheson[1] and Krayer The present report therefore will be primarily concerned with the mechanism of hypotensive action of the therapeutically useful alkaloids of *Veratrum viride* or *Veratrum album* Reference will also be made to the site and mechanism of action of biologically standardized mixtures of alkaloids of these two plant species It is considered important that such pharmacologic data be reviewed in a symposium on hypertension because numerous errors as to the pharmacodynamics of these alkaloids continue to appear in the clinical literature

NEUROPHYSIOLOGIC MECHANISMS CONCERNED WITH THE REGULATION OF ARTERIAL BLOOD PRESSURE

An understanding of presently accepted concepts of such neurophysiologic mechanisms seems pertinent prior to embarking upon a discussion of the sites and mechanisms involved in vasodilatation by Veratrum alkaloids Uvnas[3] in reviewing the role which sympathetic vasodilator (cholinergic) fibers play in the regulation of systemic blood pressure concludes "that the sympathetic vasodilator nerves are not involved in depressor reflexes or in other vascular reactions associated with the regulation of the blood pressure Such vasodilator reactions are considered to be produced by inhibition of vasoconstrictor tone" Folkow[4] in his review on Nervous Control of Blood Vessels states As previously mentioned the parasympathetic fibers are in all probability not engaged in the baro- and chemoreceptor control of the blood vessels" (p 653) He also states "The vasoconstrictor fibers can therefore be looked upon as the main neurogenic adjustors of the peripheral circulation showing prompt and often regional adjustments of their tonic discharge to any change of environment that may affect central sympathetic structures especially then the vasomotor center in the oblongate medulla" (p 647) Following this it now becomes necessary to present valid data which can point to the mechanism of action of the Veratrum alkaloids

SITES AND MECHANISM OF BLOOD PRESSURE LOWERING BY VERATRUM ALKALOIDS

It must first be noted that not all Veratrum alkaloids act by the mechanism to be discussed However all therapeutically useful pure Veratrum

alkaloids or mixtures of such act by the mechanism to be described Examples of available therapeutically useful alkaloids or mixtures the method of controlling their potency and trade names and their source of supply are presented in Table 1 Simplified diagrams of sites of action of the therapeutically useful Veratrum alkaloids have appeared in numerous publications The purpose served in presenting a diagram in this discussion is only to correct misconceptions that have appeared Because parasympathetic sites of action have been ascribed to the agents under discussion it becomes necessary for such misimpressions to be corrected with adequate experimental support

TABLE 1 AVAILABLE THERAPEUTICALLY USEFUL VERATRUM ALKALOIDS OF STANDARDIZED MIXTURES

ALKALOID OR MIXTURE	POTENCY CONTROL	TRADE NAME AND SOURCE
Protoveratrine A	Chemical assay	Protalba *Pitman Moore*
Protoveratrines A and B	Chemical and individual assay	Veralba Pitman Moore
Protoveratrines A and B	Chemical and individual assay	Provell Maleate Eli Lilly
Cryptenamine	Biological assay	Unitensen Irwin, Neisler
Alkavervir	Biological assay	Veriloid *Riker Laboratories*

Neuroanatomic and neurophysiologic data fail to support the existence of adequately widespread areas sufficient to influence vascular beds of sufficient magnitude so as to alter the total peripheral resistance (Folkow) In addition all of these postganglionic sites are atropine sensitive Ancillary pharmacologic data support these observations since if there were a balance being maintained between the parasympathetic and sympathetic control of vascular tone atropine should cause hypertension which it does not Figure 1 demonstrates the chief known sites at which antihypertensive drugs act

EXPERIMENTAL OBSERVATIONS IN DOGS WITH PROTOVERATRINE A

Four dogs were selected to provide information as to sites of action of this drug In Figure 2 A the percentage of fall in blood pressure produced by protoveratrine A is demonstrated When these dogs were vagotomized the results seen in Figure 2 B were noted no essential difference was evident between these responses and those of the dogs when their buffer nerves were all intact However when the carotid sinus nerves were severed it would seem evident that protoveratrine A lowered arterial blood pressure by stimulating the baroreceptors in the carotid sinus Note that in these four dogs when both sets of baroreceptors were denervated this drug now produced hypertension (Fig 2 C) If other pertinent experiments had not been performed the conclusion to be drawn would be that protoveratrine A lowers blood pressure by discrete stimulation of the carotid sinus baro-

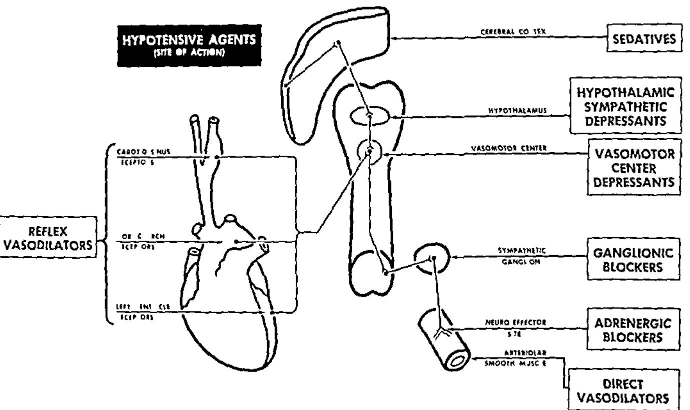


Fig 1 Chief sites of action of hypotensive drugs

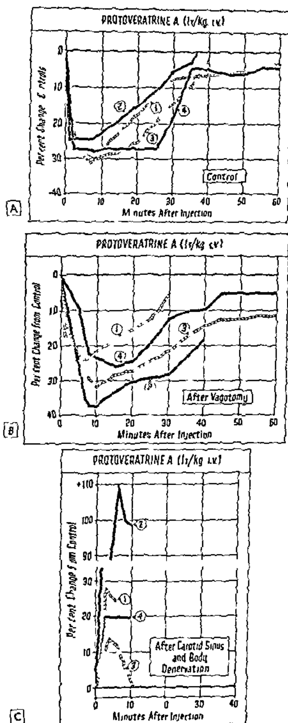


Fig 2 A B C Four dogs pentobarbital anesthesia Ordinates per cent change in blood pressure from control after protoveratrine A in intact vagotomized and carotid sinus denervated dogs

receptors However Figures 3 A and 3 B serve to contradict this thesis If in a given dog the carotid sinus nerves are sectioned first and the vagi are allowed to remain intact, one notes a fall in blood pressure from protoveratrine A this then is obliterated by section of the vagi (Fig 3 A)

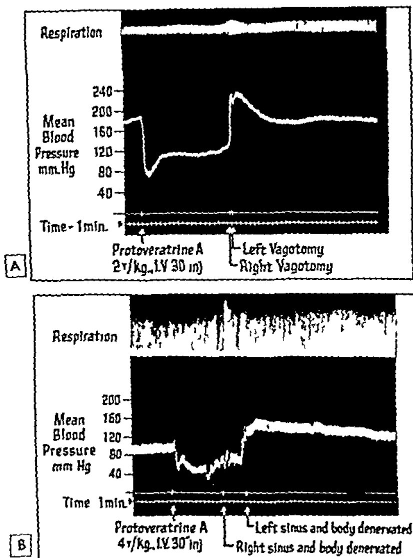


Fig 3 Dog Morphine urethane anesthesia
A Carotid sinus nerves sectioned then protoveratrine injected Vagotomy obliterates the vasodepression B Vagi sectioned in neck then protoveratrine injected Carotid sinus denervation obliterates the fall in blood pressure

When the converse is performed and the vagi are sectioned prior to drug administration hypotensive effects still appear (Fig 3 B) These too were then obliterated by bilateral vagotomy Without doubt this type of experiment demonstrates that baroreceptors from both aortic and carotid sinus areas must be obliterated in order to reveal their sites of action

Such well defined effects serve now to negate statements that protoveratrine A acts by parasympathetic stimulation (See Fig 1 in Lindley *et al*[5]) Any reflex parasympathetic stimulant effects appearing such as cardiac slowing can be obliterated by atropine or vagal section but in no way is the vasodepressor action obtunded Similar observations have been noted for alkavervir by Gruzhit Freyburger and Moe[6] and for cryptenamine in our laboratories None of the therapeutically useful Veratrum alkaloids or mixtures presently available have been demonstrated to lower arterial pressure by other than this mechanism

Confirmation that their action is partly at carotid sinus receptors is to be found in the excellent neurophysiologic studies of Dontas[7] in which he noted the rhythmic sinus nerve activity correlated with each cardiac systole changing to continuous firing during complete cardiac cycles

It should be finally emphasized that extrapolation of data on mechanism and site of Veratrum action to specific alkaloids will be fraught with error since Gruzhit *et al* have shown as have we that veratridine is without effect on these two baroreceptor sites and acts on some "higher site in the nervous system

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The Pharmacology of Hydralazine*

HENRY A SCHROEDER

Dartmouth Medical School and Brattleboro Retreat

Hydralazine or 1 hydrazinophthalazine is a unique drug unique in several respects It (and its close chemical relatives) has the curious ability to dilate constricted vascular smooth muscle for a long period of time In hypertensive man it lowers blood pressure while simultaneously increasing renal blood flow These two characteristics make it an ideal agent for the treatment of severe arterial hypertension Furthermore it is the only drug known so far which can cause a syndrome identical to disseminated lupus

* Prepared under a grant in aid from the American Heart Association

erythematosus in man and in experimental animals Therefore knowledge of its basic chemical reactions may help understanding not only of smooth muscle physiology and physiopathology but also of collagen disorders

HISTORICAL

1 Hydrazinophthalazine was first synthesized and tested in the Ciba Laboratories at Basle Switzerland by Gross Druey and Meier as one of a series of experimental antihistaminic agents containing a hydrazine group[1] As it turned out this compound and its active derivatives were not anti histamines Injection into animals caused long acting depressor responses unlike those of any hitherto known drug

The experimenters were quick to recognize the potentialities of such an agent and extensive screening tests for its primary site of action were con ducted By progressive sectioning of the brain and brain stem it was discovered that the drug no longer acted when the vasomotor center was severed from the spinal cord therefore a medullary or cerebral site of action appeared possible Further evidence in confirmation came from cross transfusion experiments between donor bodies and recipient heads of dogs showing that some although slight fall of blood pressure occurred in the body of the animal whose brain received blood from a donor dog[3] Lost sight of was the fact that spinal animals (and dogs whose heads are connected to their bodies only by nerves) are in a state of vasodilatation further work showed that hydralazine acts only upon *constricted* blood ves sels constricted by any one of a large number of agents and does not further dilate dilated vessels[4,5] The erroneous impression that hydralazine has a large central nervous action has unfortunately persisted in the minds of some investigators unfamiliar with subsequent experiments by the Basle group

Reubi was the first to give the material to human beings[6] On his return to Switzerland after a year working in our laboratories he became impressed with the peculiar property of this agent in lowering blood pressure and increasing renal plasma flow a property shared by no other agent save pyrogen and one for which we and others had searched for many years He gave 8 to 20 mg subcutaneously to six hypertensive patients four nor motensive subjects and two with chronic glomerulonephritis Diastolic pres sure fell (even with this small dose) in four hypertensives and three normo tensive subjects and one nephritic subject in all renal plasma flow increased (average 38 6 per cent range 16 to 68 per cent) with constant decrease in filtration fraction the duration of the changes being one to two hours or more

When Reubi sent his manuscript to us for publication in August 1949 we in common with a number of others had a supply of this agent on our shelves untouched We soon gave it by intravenous or subcutaneous injection daily to eight renal hypertensive dogs The prolonged effect upon blood pressure was so striking lasting twenty four hours or more that in two dogs the material was given only every other day in order to avoid excessive hypotension[7] Because the dogs remained well during a month s observation chronic experiments in hypertensive patients were begun Fortunately the first few patients to whom it was given all with nephrogenic or malignant hypertension tolerated the drug well and showed significant

reductions in blood pressure and symptomatic improvement [8] If some of the severe individual reactions notably intractable headache encountered in other patients had appeared at the onset of the study we could not justifiably have continued to use the agent with any degree of optimism

At that time it was believed to be just another sympatholytic agent and two groups of investigators Grimson Chittum and Metcalf [9] and Fries Mackay and Oliver [10] tested it against various sympathomimetic drugs and adrenergic procedures Their results differed in showing little or none and some sympatholysis These differences of opinion continued during human experiments but have been largely resolved by time and understanding of the drugs primary mode of action No prolonged effects upon the hyper tensive process were noticed during these studies

The first study on the prolonged antihypertensive effects of this agent in man was reported in abstract form in May 1951 [8] and presented in June 1951 [11] after almost two years experience About two thirds of patients were benefited but strict normotension was achieved in only a few Subsequent studies by others confirmed these results Shortly after that in July 1951 the first ganglionic blocking agent became available which when given with hydralazine provided a method for achieving strict normotension in almost every case of severe hypertension Therefore sustained interest in the pharmacodynamics of this agent declined as therapeutic results im proved Hydralazine remains however the backbone of some therapeutic regimens effective against severe hypertensive disease

CHEMICAL REACTIONS

1 Hydrazinophthalazine (hydralazine) 1 4 dihydrazinophthalazine (Nepresol) and 1 hydrazino-4 methylphthalazine enter into a number of chemical and biochemical reactions most of them of interest for the problem of their modes of action

1 Chelation The first injectable hydralazine solutions were supplied in metal and rubber capped bottles Perry noticed that the metal (iron) caps were quickly corroded and decided to test the agent with various metals As this phenomenon was noticed before the word "chelation be came popular metal binding was estimated by measuring the inhibition of the color produced by the hydralazine ninhydrin reaction [1] Of the essen tial metals Cu^{++} Fe^{+++} Mn^{++} and Fe^{++} were bound in varying amounts in that order Fe^{+++} apparently oxidized the terminal nitrogen of the hydrazine liberating 0 84 mg atoms of nitrogen pervanadyl ion liberated 1 58 mg atoms of nitrogen per millimole of drug suggesting that both terminal nitrogens of the hydrazine were oxidized In both cases the metal was probably reduced

Some abnormal" metals were likewise bound Sn^{++} (completely) Ag^{+} and Hg^{++} Alkali metals and alkaline earths were inert as were Zn^{++} Pb^{++} Cd^{++} Al^{+++} Al^{3+} Cr^{+++} and Co^{++} Both V^{+++} and V^{+} were bound strongly [13]

2 Certain carbonyl compounds were bound by hydralazine pyruvic acid acetaldehyde and (slightly) α ketoglutaric acid but not glucose lactic acid nor propionic acid [13] This reaction is common to several hydrazines

3 Mercaptans were bound reversibly cysteine reduced glutathione as

well as 2 3 dimercaptopropanol (BAL) and many other nonphysiologic substances Binding could be broken by the presence of heavy metals having a high affinity for sulfhydryl compounds Disulfides were inert [13]

4 Also inert were all primary amines and amino acids tested including arterenone the β carbonyl derivative of norepinephrine which might be expected to be bound Lyophilized angiotonin was bound while that supplied in solution was not Pherentasin was directly inactivated There was no demonstrable chemical reaction with vasopressin

5 Hydralazine combines slowly with serum protein egg albumin mashed arterial tissue and certain polypeptides (peptones) when incubated It does not combine with casein or mixed amino acids perhaps the low cysteine content of casein accounts for this difference The complex formed with certain proteins is no longer depressor nor is it able to counteract the constriction caused by barium chloride or histamine but it still retains a direct dilating action on the coronary arteries [14]

Some of these basic reactions are of biologic significance others may not be In man there was no demonstrable diminution in circulating pyruvate levels after the drug had been given in large amounts for a long time On the other hand the urinary content of hydralazine was found to be partly in the free form partly bound to urinary mercaptan As therapy was continued the ratio of sulfhydryl bound to free drug decreased i e more and more drug was excreted unbound At 20 days the amounts of both types were about equal When BAL was injected into patients all of the drug excreted was in the bound form [15]

Analyses of urine for eleven trace metals failed to show any consistent change of excretion during the initiation of hydralazine therapy On the other hand a comparison of urinary excretions of trace metals in hypertensive patients before and long after therapy had been begun showed that the abnormal pattern of hypertensive urine had changed toward but not always to normal especially as regards Mn Mo V Cd Pb Sn and Ag without change in urinary Zn Ti Cr or Ni [16]

The ability of hydralazine and its active derivatives to complex copper into a chelate is amply demonstrated by experiments on the isolated rabbit heart by Jaques Tripod and Meier [17] Copper sulfate ($1 \times 10^{-}$) was found to be constrictive on the coronary vessels Hydralazine and other substituted hydrazines capable of forming chelates completely abolished the copper induced constriction as did many copper binding agents That this may not be their sole modes of action is suggested by the inherent quality of the agents themselves in dilating the coronary arteries however all dilators tested were the metal binding agents thiourea phenylthiourea thiocarbamate 8 hydroxyquinoline cysteine methionine histidyl histidine adenosine adenosine-3 phosphoric acid -5-phosphoric acid 5-triphosphoric acid (ATP) semicarbazide hydroxylamine iso-nicotinic acid isopropyl hydrazide and four substituted hydrazines Inasmuch as of the metal ions examined Cu^{++} Fe^{++} Fe^{+++} Co^{++} Mn^{++} and Ni^{++} only Cu^{++} constricts the coronaries one is forced to the conclusion that coronary dilatation so produced is probably caused by the chelation or binding of a trace metal in the smooth muscular wall

Of the essential trace metals copper comes under greatest suspicion as an effector for coronary constriction By another and more indirect series of

experiments copper or nickel was suspected of being involved in the renal hypertension of rats for chelates of metals and ethylene diamine tetra acetate with stability constants lower than that of copper were depressor and those with higher stability constants were not[18]

Hydralazine has some interesting actions on certain enzymes, for it can both stimulate and inhibit On diamine oxidase (histaminase) it is a strong inhibitor in concentrations as low as 10^{-6} having this common property with other hydrazines hydrazine like substances and guanidines[19] Histaminase from both animals[0] and plants (red clover seedlings)[1] are affected Nepresol being the stronger agent in the case of plant enzyme There are two possible explanations for this action There is some evidence that histaminase requires pyridoxal phosphate as a cofactor In that event a metallic cofactor is probably also required for the pyridoxal amino acid or amine complex probably present as a coenzyme is a good chelating agent Inhibition could therefore be the result of chelation of metal by the drug or of the formation of a hydrazine pyridoxal compound (containing metal) such as is known to be formed with iproniazid another hydrazine[20]

Dihydroxyphenylalanine (DOPA) decarboxylase is partly inhibited by hydralazine (10^{-4}) as well as by a number of other hydrazines The relatively strong DOPA decarboxylase inhibition by a number of substituted hydrazines first reported in our laboratories[3] has been confirmed[1] Nepresol is active in lower concentrations (10^{-6})[4] DOPA decarboxylase is a pyridoxal enzyme with zinc as a cofactor inhibition may occur through chelation of zinc (although Zn complexes poorly with hydralazine) or through formation of a pyridoxal hydrazine complex

Hydralazine also inhibits histidine decarboxylase from guinea pig kidneys in relatively low concentrations (10^{-5})[-1] As histidine decarboxylase is a pyridoxal enzyme probably requiring a trace metal as a cofactor the mechanism of inactivation may be similar to that of DOPA decarboxylase

Polyphenol oxidase (tyrosinase) a copper enzyme is not inhibited by the drug which at first glance seems strange for copper complexes strongly with hydralazine and is rather loosely bound to the protein of the enzyme However the copper on the enzyme protein is in the monovalent state while in the chelate it occurs as Cu^{++} Succinic dehydrogenase and cholinesterase are also unaffected

Monamine oxidase activity was enhanced about 160 per cent by concentrations of 10^{-3} molar and about 10 per cent by 10^{-4} molar hydralazine and Nepresol This fairly strong enhancement is not shared by any other known organic substance although a slight effect in this direction is produced by *β mercaptopropionic acid, sodium nitroprusside and sodium* azide[4] This property makes these two hydrazines unique substances

There is some confusion in the literature as to whether hydralazine enhances or inhibits the action of monamine oxidase In our laboratories using enzyme from guinea pig kidney and tryptamine preliminary experiments showed inhibition[3] but later with refinement of techniques and with the use of older guinea pigs it regularly enhanced activity as did Nepresol while other substituted hydrazines inhibited activity in varying but usually concentrated amounts (10^{-} to 10^{-3}) *Iproniazid as previously found by* Zeller[-] was somewhat more strongly inhibitory On the other hand Werle Schauer and Hartung[1] found variable but weak inhibition of guinea pig

liver and tyramine activity by all the substituted hydrazines tested including two which inhibited in our experiments There was no inhibition in vivo Naess and Skramstad (quoted by Werle *et al* [1]) also showed inhibition of the enzyme from rat liver However inhibition varied greatly and was some times absent it was larger in the winter than in the summer Obviously local differences in animals their ages and possibly their states of nutrition may have caused these divergent results

The action *in vitro* of hydralazine on human pherentasin and animal hy pertensin is of considerable interest to the problem of hypertension After mixing of the two substances inactivation occurs and constriction of the isolated aortic strip no longer takes place [8] That this reaction is a direct one on the constrictor substance and not one merely of the effect of hydrala zine on the smooth muscle itself is shown by the rate of inactivation inhibi tion takes from one half to four hours to be complete and is progressive in that interval [6] In the anesthetized rat hydralazine in small doses effec tively blocks the pressor action of pherentasin while larger doses are re quired to block that of animal hypertensin [13] When pherentasin can be regu larly extracted from human hypertensive arterial blood reduction of blood pressure by treatment with hydralazine is regularly associated with disap pearance of pherentasin in subsequent blood samples [6]

If we are to learn anything from the known basic chemical reactions of the substituted hydrazines which will further understanding of vasospas tic states directions for investigating biologic phenomena are clear

1 These drugs chelate certain but not all trace metals copper being the strongest bound

2 These drugs directly inactivate two decarboxylases both probably pyridoxal enzymes containing metallic coenzymes

3 These drugs in our hands stimulate monamine oxidase

4 These drugs directly inactivate the two peptide pressor substances believed to be involved in hypertension and cause the disappearance of one of them pherentasin from human hypertensive blood

If such actions occur *in vivo* the net result would be lessened renal pro duction of vasoactive primary amine increased destruction of primary amine and inhibition of humoral peptide induced vasoconstriction

It is an interesting coincidence that those hydrazines which by struc ture do not form a five or six membered chelate ring the most stable form of chelates [7] with nitrogen as its ligands to metal are not antihypertensive nor dilator substances in man or experimental preparations On the other hand those which do form stable chelates are active This coincidence lends further confirmation of the belief that hydralazine s basic action is that of chelation of a trace metal possibly copper in the smooth muscle cell of the arterial wall

PHARMACOLOGIC ACTIONS

Although at first hydralazine appeared to be just another sympatholytic or adrenolytic agent (for long acting smooth muscle relaxants were virtually unknown at that time) experiments soon proved that any blockade exerted by the drug was not a specific adrenergic effect Arterial beds constricted by such a variety of substances as norepinephrine ephedrine ergotamine privine histamine, vasopressin and barium salts were dilated [4] the effect lasting many hours while the pressor effects of pervanadyl ion cadmium

barium pherentasin hypertensin isoamyl amine tyramine arterenone epinephrine and norepinephrine were inhibited the first four strongly and the last six less strongly [13] The indolic amines tryptamine and 5 hydroxytryptamine (serotonin) when pressor were unaffected or enhanced in activity Therefore while misleading conclusions could be and were drawn regarding the locus of activity of the drug with any one substance the only valid interpretation of all the data was that the smooth muscle cell of vascular tissue was relaxed Thus the drug resembles the nitrites thiocyanates nitroprusside azides and probably BAL certain mercaptans and other vasoactive chelating agents in its mode of action, [9] differing from most of them only in that the effect is long lasting

Such a conclusion was fortified by experiments with the spirally cut rabbit s aortic strip which is a relatively pure preparation of reactive smooth muscle The constrictor activities of the two vasoactive polypeptides hypertensin (obtained from animals) and pherentasin (obtained from hypertensive patients) were blocked by minute doses of hydralazine while much larger ones were required to inhibit the actions of norepinephrine epinephrine tyramine and isoamylamine [6] (vasopressin is inert interestingly enough in this preparation) Pherentasin was more sensitive to the action of the drug than was hypertensin

Although the primary action of the drug is on some process operating in constricted smooth muscle the relaxation is not the result of toxicity or smooth muscle poisoning Vessels and vascular beds react to stimulatory mechanisms with normal but reduced responses in its presence Vessels dilated because of denervation no longer dilate further Vascular smooth muscle preparations can be readily washed free of drug unlike their behavior with dibenamine and restored to full activity

In isolated vascular beds which are naturally relaxed little or no activity is exhibited by the drug unless vasoconstriction is induced by one of a variety of agents [4] In the isolated rabbit and cat heart coronary arteries are dilated while the amplitude of contraction is decreased [5]

Vascular beds of intact animals respond uniformly by vasodilatation Renal femoral digital splanchnic cerebral beds respond to the drug by decrease in vascular resistance [2 4] This agent is unique in prolongedly dilating renal blood vessels in the face of lowered blood pressure The other unique action is that once full vasodilatation is achieved by the drug subsequent doses produce no further effect [1] A floor" is reached

Smooth muscle from organs other than blood vessels is variously but less strongly affected by hydralazine than is that of blood vessel [8] Rabbit intestine is paralyzed by concentrations of 10^{-5} while guinea pig uterus and seminal vesicle is unaffected at concentrations of 10^{-4} On the rabbit intestine there is some antagonism to the action of barium chloride (10^{-3}) but none to that of acetylcholine antagonism to histamine on guinea pig intestine and to epinephrine on guinea pig seminal vesicle occurs at 10^{-4} concentration Thus other types of smooth muscle than vascular are much less sensitive to the action of hydralazine for antagonisms in the isolated rabbit and cat heart to the coronary constrictive effects of vasopressin barium chloride and histamine and to the dilating action of epinephrine are seen at concentrations of 10^{-8} to 10^{-7} hydralazine The antagonistic effects of the drug on the actions of various constrictor agents in the isolated vessels of rabbits hind limbs are in decreasing order of potency histamine seroto

nin vasopressin barium chloride norepinephrine and epinephrine These and other considerations have led Tripod and Meier[5] to suggest that the substituted hydrazines act on some metal or metals concerned in enzymes having to do with vasoconstriction[30]

These effects add up to an agent theoretically ideal for the treatment of generalized vasospastic states There is one effect which detracts from this ideal tachycardia Increase in rate is produced in rats cats dogs rabbits and man

In normotensive human subjects acording to Wilkinson Bachman and Hecht[31] hydralazine given in brief experiments does not alter systolic blood pressure significantly but lowers diastolic pressure moderately increases cardiac output and rate considerably and increases renal plasma flow with a consequent decrease in the fraction filtered through the glomerulus Pulmonary vascular resistance is decreased The pressor responses to pain induced by the hand in ice water and to the Valsalva maneuver are inhibited Skin temperature rises and when the drug is given intra arterially it rises only on the injected side Digital blood flow is increased

The effects of this drug in hypertensive patients differs in several respects from that seen in normotensive subjects While renal plasma flow cardiac rate cold pressor and Valsalva responses digital blood flow and skin temperature are altered in the same direction as in normotensives cardiac output is only slightly increased (15 per cent as much) and both systolic and diastolic pressures fall markedly Therefore in the broad sense of the term this agent appears to be specific for hypertension in so far as blood pressure is concerned lending further basis to the belief that it is a true antihypertensive substance As such it comes closer to being an ideal agent than does any other known drug

Thus the substituted hydrazines capable of forming stable metal chelates have two unique actions (a) Constricted vascular smooth muscle is prolongedly dilated and (b) there is a maximal dose response curve beyond which further dilatation cannot be achieved even by huge doses of the drug Therefore these drugs appear to act by wiping away so to speak one mechanism basic to muscular contraction of vessel walls It is probable that all of the other pharmacologic actions of the drugs such as their antagonisms to sympathomimetic and adrenergic stimuli and their slight effect on the central nervous system can be explained as indirect effects of this basic action

CLINICAL ACTIONS

Prolonged oral administration of hydralazine results in a significant reduction of blood pressure in about two thirds of hypertensive patients a reduction which is sustained as long as the drug is given properly Because of the induction of tachycardia and minor side effects this agent is seldom used as the sole therapeutic agent almost always it is combined with another agent acting on the autonomic nervous system In hypertensive emergencies however such as hypertensive encephalopathy ("wet brain") in malignant hypertension toxemia of pregnancy and acute nephritis it is a valuable hypotensive agent when given parenterally for hours or days[3]

The fate of the drug in the body is unknown After a single oral dose of 50 mg 2 9 per cent (range 1 0 to 4 4 per cent) was excreted in the urine[15] Half of the recovered amount appeared within 2½ to 5 hours and the remain

der within 24 hours Effective blood levels in adequately treated patients receiving 600 mg per day ranged from 0 06 to less than 0 005 mg with a mean of 0 023 mg per 100 ml plasma In uremic patients values were higher up to 0 04 mg per 100 ml in one individual receiving huge doses the value was 1 0 mg Recovery of the free drug in the urines of adequately treated patients studied for three to five weeks in hospital varied from 2 0 to 0 3 per cent with a mean of 1 1 per cent while total urinary drug (free + sulfhydryl bound) ranged from 6 6 to 0 4 per cent with a mean of 2 7 per cent of the amount ingested Thus most of the drug is metabolized but if urinary levels are any criterion of blood levels excretion and metabolism or conjugation is relatively rapid The lesson to be learned from the data is that the drug must be administered at frequent intervals every four hours (omitting one night dose) has been our practice for many years Measurements of blood pressure after a single oral dose bear out these observations for the effect lasts only one to four hours

Balance studies on the drug have suggested that gastrointestinal absorption is good and the ratio between effective parenteral and oral dosages appears to approximate unity Urinary excretion of parenteral drug is about the same as that of oral drug

No recommendations as to dosage can be given for any antihypertensive drug The dose is the amount which will produce the effect desired without undue toxicity The severity of hypertension varies widely from case to case In general an upper limit of 1 0 gm per day can seldom be tolerated for long 500 mg per day seems to be an optimal level in most severe cases and sustained effects are seldom significant when less than 300 mg per day is ingested

Actual tolerance to hydralazine rarely occurs As a matter of fact in our experience no case of tolerance has appeared when the drug has been given continuously although initially effective small doses had to be increased[7] With time (six months or more) and sustained normotension (mean 140/90 mm Hg or less) the maintenance dose of the drug could usually be decreased and in some cases omitted altogether[33] On the other hand when hypertension was severe and therapy was intermittent (using hydralazine and ganglionic blocking agents) tolerance was the rule[34] To date no satisfactory explanation of this phenomenon has been put forward in terms of either the drug's primary mode of action or the body s response to it[35]

There is no doubt whatsoever that the mortality rate of severe and malignant hypertension can be considerably reduced by the concurrent use of ganglionic blocking agents and hydralazine in adequate doses In fact by any number of classifications of the severity of the disease long term survival rates are more than doubled as compared to the best surgical management (lumbodorsal sympathectomy)[36] while even in malignant hypertension which has progressed to azotemia (which uniformly has a short survival period and which neurosurgeons usually exclude from operative procedures as poor risks) the four year death rate is halved Presumably survival rates of less severe types will eventually be found to be considerably higher when enough time has elapsed to verify preliminary impressions

SIDE EFFECTS AND ACTIONS, MINOR AND MAJOR

When hydralazine is given alone certain acute side effects appear in a

small percentage of patients some of which are explicable by its known mode of action and some of which are not

Because many of the hydrazines are histaminase inhibitors [19] it is likely that some of the immediate reactions are caused by slight excesses of histamine generally or in local areas *Severe to mild headaches mimicking* those induced by histamine are not uncommon they are less frequent and severe if a ganglionic or sympathetic blocking agent is first given Flushing and in some individuals the diencephalic flush which can be induced by intradermal histamine[37] may appear for several days Generalized slight edema without gain in weight but with swollen fingers and eyelids stuffiness of the nose and aching of the back may disturb the patient Rarely a flu like syndrome comes out full blown with slight fever especially during the winter months These reactions disappear in a few days while the drug is continued Rarely however repeated pyrexia chills prostration malaise and headache have interdicted the use of the drug

Other effects good or bad appear after prolonged administration of the drug Plasma cholesterol levels are lowered significantly for as long as three years [38] this effect is also seen with another chelating agent and is not considered a manifestation of toxicity A slight degree of secondary anemia easily responding to ferrous salts occurs in a majority of patients possibly because of the ability of hydralazine to chelate and reduce iron The conjunctivae appear slightly injected for several years During the fall months summer tan seems to fade very slowly or not at all

In most patients angina pectoris is relieved by the drug given in association with a ganglionic or nerve blocking agent Occasionally it is made worse a fact easily explicable in terms of knowledge of the atherosclerotic process coronary blood flow and the action of hydralazine on the coronary and peripheral arteries [35] *

The most serious and yet the most interesting late toxic manifestation is the development of *reversible* disseminated lupus erythematosus in somewhat less than 10 per cent of patients This syndrome occurs in from 5 to 24 months of continuous administration of hydralazine and is more apt to appear in patients taking more than 400 mg per day than in those taking less The L E cell is found in the peripheral blood of severe cases (those who have continued ingestion of the drug long after the first attack of arthralgia) and some or all of the bizarre local and systemic manifestations of disseminated lupus take place in their usual irregular regularity [39, 40, 41, 42]

The first premonitory sign is often low normal levels of blood pressure the second is usually arthralgia The only differentiating features of the drug induced from the true disease are its reversibility and rather rapid reversibility when the drug is discontinued and recurrence when the drug is readministered Renal damage however presumably of lupus nature may *occur rarely when resulting in azotemia the changes are presumably per*manent Deaths have been reported only in those patients who have not been continuously under the care of physicians who recognized the syndrome [43]

In our laboratories Comens has reproduced what is apparently lupus in dogs by feeding hydralazine daily [44] The mechanism which produces the L E cell can be demonstrated in the peripheral blood using dog serum and

* Hydralazine *alone* is more apt to increase angina than to relieve it especially during the initial tachycardia increase in cardiac output and fall in blood pressure and has even rarely induced myocardial infarction

human leukocytes (dog leukocytes merely form rosettes or show fragmented nuclei) Serial renal biopsies have demonstrated the development of "wire loops in the glomeruli[44] Although unconfirmed in this country when dogs were fed hydralazine five days a week (instead of daily) the L E phenomenon has been produced in guinea pigs by Siguier Betourne and Bonnet de la Tour in France[45] thus confirming Comens pioneering work

We and Dustan *et al* at the Cleveland Clinic[40] have long speculated as to whether or not "hydralazine disease represents a depletion phenomenon or a true sensitivity reaction It has some characteristics of both conditions For example three years after recovery from the disease the peripheral blood of a patient has been found loaded with L E cells a week or two after readministering small doses of hydralazine suggesting sensitivity to the drug On the other hand reduction of dose may cause partial regression of symptoms and signs for many months arguing more for a state of partial depletion of some vital substance The sole clue, and a poor one at that is found in analyses of urine for trace metals low Mn Mo Pb and elevated Zn and Sn were found with the exception of high Pb similar findings occurred in the urines of five cases of disseminated lupus We have been unable to affect the condition by feeding massive doses of vitamins especially pyridoxal hydrochloride or essential trace metals notably Cu^{++} and Mn^{++} *The pathogenesis remains a mystery but its elucidation will probably result* in partial understanding of that of true disseminated lupus

SUMMARY

Hydralazine and its active derivatives are unique vasodilator agents They prolongedly dilate only constricted blood vessels and once they have acted further doses cause no further effects Apparently they affect some basic mechanism in the vascular smooth muscle cell concerned with vasoconstriction As chelating agents there is evidence that they act by complexing some trace metal so concerned possibly copper

In hypertension they directly inactivate hypertensin and pherentasin and chronic administration causes the disappearance of the latter from blood They have the unique property of increasing renal plasma flow in the face of a lowered blood pressure As true antihypertensive agents of moderate potency at present they form the basis of chemical therapeutic regimens successful in lowering elevated blood pressure to normal levels more or less permanently

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Discussion

JOSEPH DIPALMA *Moderator*

BENEDICT ABREU	SIBLEY HOOBLER
RALPH FORD	EDWARD MEILMAN
EDWARD FREIS	JOHN MOYER
STANLEY GITLOW	WILLIAM PATON
ARTHUR GROLLMAN	H MITCHELL PERRY
CARROLL HANDLEY	ALBERT PLUMMER
WILLIAM HOLLANDER	HENRY SCHROEDER

DR DIPALMA One of the major points that I think has been developed this morning is that a pure centrally or peripherally acting drug does not exist As a matter of fact we might say that we would probably have great difficulty in defining accurately what is a centrally acting drug and what is not For example we might say that a centrally acting drug is one which loses its activity in the spinal animal but we already have received evidence that the activity of the drug can be completely missed if we use a spinal animal It happens to be a very unphysiologic preparation

Dr Plummer in therapeutic doses as used in hypertension is the blood pressure response to the Rauwolfia alkaloids due to the release of catechol amines in the brain or is it due to some other effect?

DR PLUMMER As I tried to indicate in my discussion this is a highly controversial point and I think it is not possible to give a definitive answer but on the basis of the evidence as it is accumulating now I would say that the peripheral effect is probably much more important than we had previously realized Five years ago when reserpine was first used the central effect was the only effect which was known and hence its action was attributed to that effect but on the basis of the pharmacologic evidence which has been presented to us during the last couple of years it is not possible to ignore the peripheral effects Both effects are important In addition it is not unlikely that in certain clinical cases the sedative effect of reserpine might be quite desirable

DR DIPALMA Do any members of the panel wish to take issue or add to this?

DR SCHROEDER This morning we saw some slides of Dr Moyer's that showed a definite effect after the intravenous infusion of reserpine Now what bothers me is that I saw a recent report in the *Journal of Chronic Diseases* by Dawsett and Wood and others* using the double blind technique to evaluate the response to reserpine phenobarbital and reserpine and hydralazine i e three groups of patients and there was no demonstrable effect of reserpine on the blood pressure Does that bother you Dr Plummer in view of all the reports that have come out in the last five years?

* J Chron Dis [illegible] 23[illegible] 1957

DR PLUMMER Well that would be a little difficult to explain I remember that Dr Wilkins presented some studies at the New York Academy Symposium in 1954 in which he showed the opposite He showed that when he went from reserpine to phenobarbital he lost the hypotensive effect and then with reserpine it came back Consequently I feel quite sure that this drug does lower blood pressure but to what degree I don t feel qualified to answer

I would like to interject that using spinal animals to pick up any hypotensive drugs is certainly risky business because with reserpine in the spinal animal one gets a rise in blood pressure

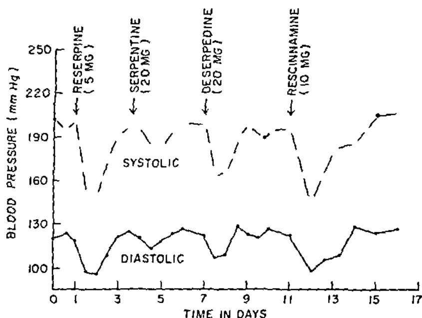


Fig 1 Blood pressure response to different Rauwolfia alkaloids The response to 10 mg of rescinnamine given parenterally is about equivalent to the response to 5 mg of reserpine Twenty mg of deserpedine is nearly as effective as reserpine and rescinnamine given in doses of 5 and 10 mg respectively Not only does the dose requirement for producing the maximum reduction in blood pressure vary but the degree to which the blood pressure can be reduced also varies

DR MOYER Certainly you would not question the hypotensive potency of Rauwolfia alkaloids when given by the parenteral route Not only are the drugs effective but at maximum doses of each alkaloid there is a difference in the maximum degree of blood pressure reduction that can be obtained Figure 1 is a study that we did giving different Rauwolfia alkaloids to a group of patients on different days There was a significant difference after the various compounds

When we made observations on cardiovascular hemodynamics in hypertensive patients reduction in blood pressure was due to a reduction in peripheral resistance Despite a decrease in heart rate cardiac output did not appear to be altered

Observations on the acute effect on renal hemodynamics in patients with hypertension indicated a slight reduction in glomerular filtration rate and

sometimes in urine volume Occasionally when the blood pressure decreased rapidly there was a marked reduction in glomerular filtration rate associated with a decrease in urine volume and sodium excretion However readjustment usually occurred rapidly and prolonged effects on water and electrolyte excretion were minimal for the group

It is not as easy to draw equally definitive conclusions when the drug is given orally I should like to agree in part with Dr Schroeder in that when

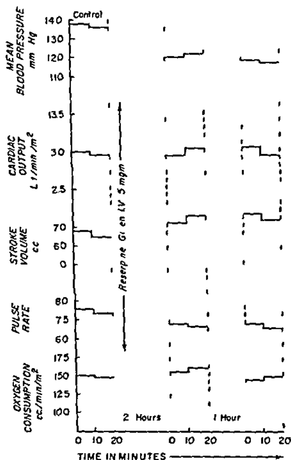


Fig 2 Cardiovascular response to reserpine given parenterally in a patient with uncomplicated hypertension Cardiac output is not altered As the pulse rate decreases the stroke volume increases (From A M A Arch Int Med 96 1 1955)

Rauwolfia is given orally in the doses that are usually employed it is not a potent hypotensive agent Nonetheless it does reduce the blood pressure to a significant degree in about half of the patients We have studied a number of different preparations and when using a drop of mean arterial blood pressure of 20 mm Hg as a significant decrease in patients with hypertension of all grades of severity the blood pressure has responded in 45 to 55 per cent of patients in each study when adequate doses were used (Table 1) The doses that we employed for these studies were 0 5 to 1 mg of reserpine 4 to 8 mg of alseroxylon 200 to 300 mg of the whole root and 1 to 2

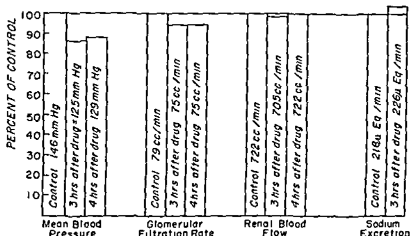


Fig 3 Acute renal hemodynamic response to 3 mg intravenous reserpine in patients with hypertension (mean values) As the blood pressure decreases there is a slight and consistent reduction in glomerular filtration rate However this is minimal and returns to the control value within 24 to 48 hours despite maintained reduction in blood pressure There is very little over all effect on sodium excretion but the response of this modality is variable If there is a significant reduction in glomerular filtration rate this may be associated with a rather marked reduction in sodium excretion in some patients

mg of rescinnamine The blood pressure was reduced below 150/100 in about 20 to 25 per cent of patients in each study and these were nearly always the patients who prior to therapy had mild and more labile hypertension Therefore there is no doubt in my mind that the drug is effective in lowering the blood pressure in many patients Except for the incidence of agitated depression side effects are similar

I would agree that the chief virtue of Rauwolfia is as adjunctive therapy with other agents which depress sympathetic nervous system activity (Fig 4) When this is done the dose requirements of such drugs as hydralazine

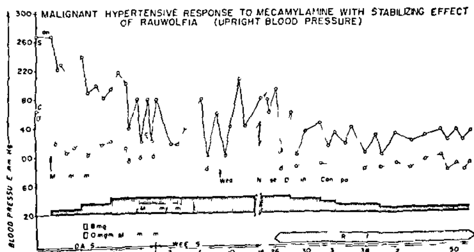


Fig 4 The effect of Rauwolfia on the response to ganglionic blocking agents Not only is the blood pressure stabilized but this occurs with a smaller dose of the blocking agent (From A M A Arch Int Med 98 187, 1956)

TABLE 1 BLOOD PRESSURE RESPONSE TO DIFFERENT EXTRACTS OF RAUWOLFIA IN PER CENT OF PATIENTS TREATED

	Control diastolic < 120 mm Hg but > 100 mm Hg (Subgroup A)			Control diastolic > 120 mm Hg (Subgroup B)			Totals (Subgroups A & B)		
	No treated	Responsive %	Normotensive %†	No treated	Responsive %	Normotensive %†	No treated	Responsive %*	Normotensive %†
Alseroxylon	69	49	43	49	53	24	118	51	36
Rauwolfia	21	52	29	21	57	14	42	55	21
Reserpine	28	46	32	34	59	6	62	53	18
Rescinnamine	42	45	19	42	50	7	84	48	13
Totals and per cent	187	51	35	159	55	14	346	53	25

Per cent of patients in this subgroup who obtained a reduction in mean blood pressure of 20 mm Hg or more from control value

† Per cent of patients in each subgroup who became normotensive (blood pressure < 150/100)

TABLE 2 ANALYSIS OF SYMPTOMATIC RESPONSES TO DIFFERENT RAUWOLFIA PREPARATIONS

	ALSEROXYLON			RAUWOLFIA (Whole Root)			RESERPINE			RESCINNAMINE		
	NUMBER COM PLAINING	IMPROVED NO	IMPROVED %	NUMBER COM PLAINING	IMPROVED NO	IMPROVED %	NUMBER COM PLAINING	IMPROVED NO	IMPROVED %	NUMBER COM PLAINING	IMPROVED NO	IMPROVED %
Symptom												
Headache	69	52	75	16	11	69	22	16	73	21	15	71
Angina pectoris	15	7	47	9	2	22	2	1	50	12	5	42
Congestive heart failure	59	8	14	16	2	13	13	2	15	22	7	32
Electrocardiogram	63	5	8	21	2	8	37	2	5	64	4	6
Fundi	11	1	9	8	0		11	0		4	1	25
Renal impairment	20	0		9	0		6	0		21	0	
Hypertension	118	60	51	42	23	55	62	33	53	84	40	48

and ganglionic blocking agents are materially reduced and consequently the side effects are less For example we studied the response to Dibenzyline given alone and in combination with Rauwolfia When Rauwolfia was given the effective hypotensive dose of Dibenzyline for the over all group of patients was only 10 per cent of the requirement observed when Dibenzyline was not given in combination with Rauwolfia In fact I think that we should go back and study the blood pressure response to the combination of Dibenzyline chlorothiazide and Rauwolfia This might prove to be a very effective therapeutic approach

Finally I might add that the response rate comparing Rauwolfia given alone with chlorothiazide given alone in out clinic patients with hypertension on an unrestricted sodium diet (using the above criteria) is about twice as great after Rauwolfia indicating that chlorothiazide is not as potent as Rauwolfia when each drug is given alone Nonetheless this does not detract from the importance of either of those agents as adjunctive therapy for use with drugs which depress sympathetic nervous system activity

DR FREIS I am impressed Dr Plummer with the difference in man when reserpine is given parenterally and orally Parenterally it seems to be a considerably more potent antihypertensive agent than orally and much of the pharmacology that you showed as Dr Schroeder indicated was after parenteral use I wonder if you could tell us what effect a dose which is comparable to the clinical oral dosages used say 02 mg/kg per day has on the nictitating membrane carotid occlusion reflex response myosis and blood pressure in the dog

DR PLUMMER If you give 02 mg/kg orally to dogs after about the third day you will notice miosis and relaxation of the nictitating membrane and after about a week the maximal blood pressure response is achieved at a level depending on whether you are dealing with a normotensive dog or a neurogenic hypertensive dog The level may drop 25 to 40 mm Hg mean arterial blood pressure and persist there as long as you keep the dog on that dose We have kept animals on reserpine in this way for periods up to two years and they are sedated in a mild sort of way

DR FREIS And how about the carotid occlusion effect?

DR PLUMMER The carotid occlusion reflex response in the unanesthetized animal is difficult to arrive at

DR FREIS May I ask you Dr Plummer do these dogs develop a tolerance to the gastrointestinal effects of reserpine? I mean the diarrhea that is produced by reserpine?

DR. PLUMMER Yes that is so The reason we worked with such small doses of reserpine i e 20 gamma/kg was that the dog is particularly sensitive to the diarrhea producing effects of reserpine It is the most sensitive species we know We found that we could start off with 15 gamma and then go to 20 25 or 35 gamma/kg before they started to get diarrhea Then when the dose was reduced and increased later they didn t get the diarrhea In that way it was possible to go up to 50 60 or 70 gamma/kg and we could carry them for quite some time but if we gave them 50 60 or 70 gamma at the beginning they would die of diarrhea

DR. MOYER Dr Schroeder raised the point as to whether reserpine actually has any real hypotensive effect referring to reports which have suggested that the drug is interchangeable with a sedative and that it depends primarily for its sedative effect rather than a specific cardiovascular response We have had occasion to study some patients who were hypertensive and who were completely anesthetized for a surgical procedure These patients remained hypertensive under the general anesthesia but when given reserpine under these circumstances they got a very dramatic reduction in blood pressure This then means to me that the drug is capable of having specific cardiovascular effects in reducing blood pressure under conditions in which a sedative certainly would be ineffective Getting back to Dr Freis point I would like to ask Dr Plummer whether he thinks that there is a different mode of action when the drug is used orally than when it is given parenterally

DR PLUMMER I dont think that there is any fundamental difference in the action whether you give the drug orally or inject it As to the mode of action Marshall and Dwight in England have shown that it is possible to get a greater release of norepinephrine from the various tissues in the body which contain it when a given dose of reserpine is given over a period of days as compared with a single dose In other words 100 gamma given over ten days is more effective than 1 mg given stat The differences are quantitative rather than qualitative when you vary the route of administration The effects are more marked on the initial day with a large single dose but if you give small divided doses just as with digitalis you reach your goal with more benefit to the patient

DR SCHROEDER Dr Plummer we at one time had characterized reserpine as the drug with fatal side effects in that in a certain percentage of patients it produced psychoses agitated depressions with suicidal tendencies This has resulted in suicide which could be called a fatal reaction How do you account for this that a drug which is used so widely to treat psychoses will produce psychoses in normal individuals? This reaction is roughly 5 per cent, maybe more in patients with hypertension

DR PLUMMER I think it hinges on the definition of the normal individual The question arises as to whether a psychosis which is produced in a person is a newly created entity in that person or whether he may have had an underlying psychosis which is made manifest In any case it certainly is real I would rather aim toward the latter view however that patients on the depressed side might tend to show this type of thing

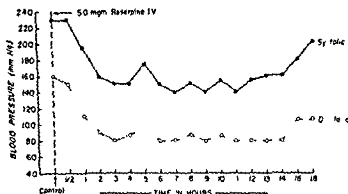
DR MEILMAN I dont find it at all difficult to think that a drug which can help psychosis can also produce it X ray can cure cancer and can produce cancer I find this a very acceptable kind of concept One question I would like to pose I am intrigued by the fact that Rauwolfia compounds are often very effective in straightforward renal hypertension in man as well as in renal hypertension in animals Yet there is nothing that I understand about its mechanism of action which helps me explain this situation

DR MOYER Figure 5 is a patient with hypertension of renal origin due to

unilateral renal artery occlusion The blood pressure in response to reserpine given parenterally is quite apparent

DR SCHROEDER It has not been my impression that it was not effective except parenterally but that oral doses were relatively ineffective

DR MEILMAN I have given oral medication to a patient with one kidney chronically contracted and she is normotensive on Rauwolfia



RENAL FUNCTION RESPONSE FOLLOWING HOMOGRAPH IN PATIENT WITH GOLDBLATT KIDNEY

	Glomerular Filtration Rate ml/min		Renal Blood Flow ml/min	
	Right (occluded)	Left	Right (occluded)	Left
Control	0	25	0	130
Blood Pressure Rx	0	35	0	200
Homograph				
1 month	0	45	0	475
8 month	0	60	0	725

Fig 5 Blood pressure response to 5 mg intravenous reserpine in a patient with malignant hypertension associated with occlusion of the left renal artery and the abdominal aorta The response was equivalent to that seen in patients with essential hypertension As the blood pressure was reduced and continued at nearly normotensive level for a prolonged period of time glomerular filtration rate in the opposite kidney (unoccluded) increased progressively so that after six months it was twice as great as it was immediately after admission when the patient was in the state of hypertensive emergency Function was reduced in this kidney 50 per cent or more on admission due apparently to the increase in blood pressure resulting from occlusion of the opposite renal artery This would seem to indicate that blood pressure elevation produces vascular damage and by reduction in blood pressure the vascular changes can be reversed (From A M A Arch Int Med 95 563 1955)

DR SCHROEDER I can't explain that except that it has some peripheral action but not in the doses given

DR DIPALMA Dr Paton would you have an opinion on that?

DR PATON I was wondering whether the peripheral effect in depleting the sympathin in the adrenergic nerve could affect some of your renal cases due

to vasodilatation Dr Plummer mentioned it but I should like to supplement his remarks by saying that reserpine is now being widely used in England whenever it is desired to inactivate a sympathetic nerve experimentally and it's proving out rather nicely

Dr Hoobler There's a lot of talk about renal hypertension supposedly not being responsive to sympathetically acting drugs I would like to take the point of view that there are at all times in all types of hypertension various regulations of the blood pressure which are continuously active To be specific with renal hypertension you can find by action potentials on the carotid sinus that there is a sympathetic vasomotor outflow which you can normally modulate by blocking agents and other procedures in the experimental animal Why would you expect renal hypertension in humans to behave differently? Furthermore in the clinic renal hypertensive patients have a normal fall of blood pressure with tetraethylammonium We found that out many years ago And you can treat renal hypertensives as John Moyer showed bringing blood pressure down to normal by a drug acting primarily on the sympathetic nervous system Therefore I don't find it a paradox I would be confused by the concept that because you had renal hypertension you could not have blood pressure elevation due to neurogenic factors

Dr DiPalma I think we should turn to another group of drugs now namely the Veratrum alkaloids Dr Abreu I'd like to know what are the disadvantages of the Veratrum alkaloids that have led to their use not being as popular as other drugs?

Dr Abreu One thing that I would like to point out is that I don't think that hypertension is treated in the same way that other diseases are treated We treat diabetes by titrating the dose All too frequently we don't treat hypertension by titration I will go on to answer the question directly and say that certainly in the case of the Veratrum alkaloids the margin between the dose that produces effective hypotension and the dose which produces side effects such as emesis is narrow But certainly a drug which acts by a mechanism such as I have described I think should be considered and given a careful trial

Dr DiPalma Do the other members of the panel wish to comment on this?

Dr Freis Since this session I believe is concerned with fundamental pharmacology I would like to ask that type of question of Dr Abreu You showed very nicely this morning that the drug acts apparently by stimulating certain afferent nerve endings in the myocardium and in the carotid sinus to produce a reflex type of vasodilatation I think this has been shown very nicely by Dr Krayer and by several others before him but what I would like to know is what do you think is the efferent arm of this vasodilator reflex?

Dr Abreu The efferent arm is primarily depression of vasoconstrictor activity That is the only answer I can give you

Dr Freis And yet what you see doesn't resemble sympathetic inhibition such as postural hypotension etc does it?

Dr Abreu I think it does Postural hypotension develops as with other sympathetic blocking agents If you want to call this a sympathetic blocking agent

Dr Hoobler I would like to support Dr Freis and ask a few more questions about this efferent arc which to me is an unexplained entity which may very well lead to useful pharmacotherapy in the future Let me cite a couple of points In the first place I would agree with Dr Fries that the response is entirely different from a total sympathetic inhibition We had a patient who absolutely did not respond to ganglionic blockade He was completely refractory You don t see that type very often He was given 40 mg or more of hexamethonium intravenously with no drop in blood pressure He did respond to Veratrum Presumably his sympathetic efferent pathway was totally blocked and yet he had a response to Veratrum I think also that in sympathectomized patients the response is just about the same as in the nonsympathectomized You might say that there are some sympathetics left in maintaining tone I am not sure that this is the story As much as I would like to go on with Dr Moyer s scheme I would like to think also of a vagal pathway or some hidden pathway that can cause vasodilatation that is not mediated over the conventional sympathetic route I have no evidence for it I hope someone in the panel or in the audience some day will develop it because I think this is a very important and a valid pathway

Dr. Abreu I think I can answer one point and that is that the vagus is not important Certainly there are cholinergic paths which Ugassis described but which she says 'have no important role in the maintenance of blood pressure The primary effect of Veratrum as far as controlling blood pressure is concerned is due to inhibition of vasoconstrictor tone Perhaps Dr Paton can give us some further points on this

Dr Paton There are two points I would like to make One is to take up Dr Hoobler s presumption that he can produce complete ganglion block I don t believe this is ever achieved in man In fact I am sure it is impossible The other point is about the other possible pathways whereby vasodilatation could occur I think the suggestion about the cholinergic vasodilators that Ugassis described is not a good one since these pathways are atropine sensitive and I understand that the vasodilatation or the hypotensive effect of Veratrum usually resists atropine although the bradycardia may be abolished But with the bradycardia abolished the blood pressure still goes down and I have taken this to rule out Ugassis mechanism As a matter of fact I at the moment would tend to back the removal of sympathetic tone because the only other pathway available is antidromic vasodilatation which is so recherche that I think one shouldn t argue about it too much

Dr DiPalma Dr Grollman do you have some comment on this?

Dr Grollman I could make some general comments In the first place I think we are jousting with windmills when we worry about central versus peripheral action It certainly is a rare drug that limits its action to a single system much less to a part of a given system What we have to do is to describe the action in terms of what we can observe

tension For example the drug lowers the diastolic blood pressure in normotensive individuals as well as in hypertensives as Dr Schroeder just mentioned Figure 6 is the response in such a patient Likewise the drug is a cardiac stimulant causing a sharp increase in pulse rate and in cardiac output in both normal subjects (Fig 6) and hypertensive patients (Fig 7) This occurs at the same time that the blood pressure decreases We have thought that this cardiac effect was due to central sympathetic stimulation

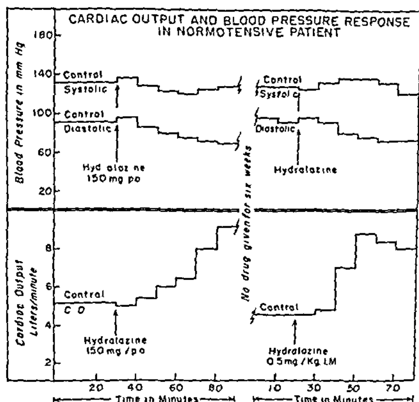


Fig 6 Cardiac output and blood pressure response to hydralazine in a patient with normal blood pressure Following an initial test dose of 150 mg given orally there was a sharp increase in cardiac output associated with the reduction of blood pressure The diastolic pressure response was more prominent than the systolic Six weeks later a test dose was given parenterally with a similar response of the diastolic pressure but there was a more abrupt increase in cardiac output associated with a slight initial rise in systolic pressure followed by a fall The onset of action was less delayed than after oral administration (From A M A Arch Int Med *91* 415 1953)

since it can largely be prevented in the experimental animal by the administration of large doses of ganglionic blocking agent (Figs 8 A and 8 B) Tolerance to the cardiac stimulant effect of a fixed dose of the drug develops rather rapidly but this response can again be activated by increasing the dose It occurs after giving the drug either orally or parenterally Palpitation is a frequent complaint and patients with coronary artery disease have been reported to have a higher incidence of anginal episodes and even myocardial infarction This effect on the cardio accelerator nerves can also be blocked with Rauwolfia

It appears to me that the renal effects are mediated through neurogenic

mechanisms also For example in Table 3 is summarized the response to injection of hydralazine into one renal artery The drug produced no alteration of blood flow on the injected side but when recirculated through the body there was an increase in blood flow in the contralateral (uninjected)

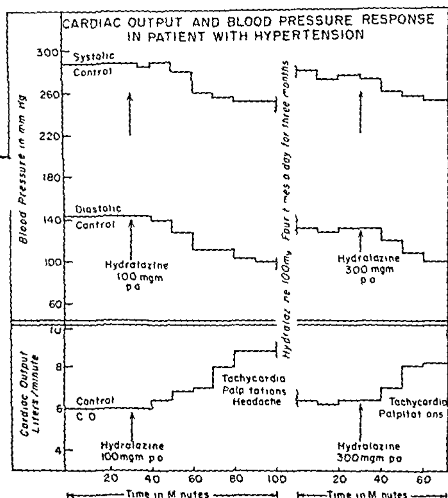


Fig 7 Cardiac output and blood pressure response to oral administration of hydralazine The patient had essential hypertension There was an *increase in* cardiac output associated with blood pressure reduction headache palpitations and tachycardia After the patient had taken the same dose four times a day for three months the tachycardia and palpitations and headache were absent and the cardiac output had returned to the control levels However the blood pressure was also increased toward the control level When the dose of the drug was increased (to 300 mg) a response similar to the initial one (100 mg) was obtained (From A M A Arch Int Med 91 419 1953)

kidney We interpreted this as a central neurogenic effect that resulted when the hydralazine got into the general circulation Of course it could be a direct response to the increase in cardiac output but certainly it didn t appear to have a vasodilatory effect in the injected kidney where drug concentration should have been greatest

TABLE 3 RENAL HEMODYNAMIC RESPONSE TO HYDRALAZINE FOLLOWING RENAL INTRA ARTERIAL INJECTION IN 8 DOGS

	GLOMERULAR FILTRATION RATE (cc min)		RENAL PLASMA FLOW (cc /min)	
	Injected kidney	Uninjected kidney	Injected kidney	Uninjected kidney
Control drug injection	40	38	210	230
1 minute	32	36	212	226
5 minute	36	40	190	234
10 minute	38	42	170	250
20 minute	42	40	160	280
30 minute	40	38	200	256

turn Calculated peripheral resistance was near to control values When *hydralazine (BA 5968) was now given there was an additional reduction in* blood pressure due to decreased peripheral resistance Cardiac output did not increase due apparently to the premedication with the ganglionic blocking agent hexamethonium

The primary significance is that neither the direct cardiac effect nor the blood pressure response to epinephrine was blocked with these rather large doses of hydralazine This would suggest that hydralazine has very little adrenergic blocking potency The clinical counterpart to this is seen in Figure 9 This was a patient who had a pheochromocytoma and who was given hydralazine at a time that we were not aware of the sympathetic effects of

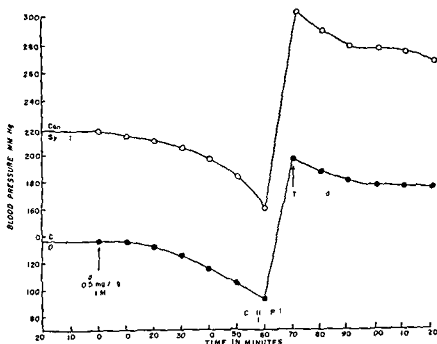


Fig 9 Blood pressure response to parenteral administration of hydralazine in a patient with a pheochromocytoma Following the initial reduction in blood pressure a hypertensive crisis was precipitated *due apparently to stimulation* of the tumor with release of epinephrine (From A M A Arch Int Med 91 419 1953)

the drug Apparently the drug stimulates the sympathetics to the adrenal medulla also At any rate the administration of this agent precipitated a hypertensive crisis in this patient It is quite conceivable that the tachycardia and palpitations seen in essential hypertensive patients given hydralazine are also due to a release of epinephrine from the adrenal medulla At any rate it seems most likely that if the blood pressure response to hydralazine were due primarily to its peripheral blocking action this sort of reaction would not occur

Dr Schroeder referred to the increase in renal blood flow as helping to

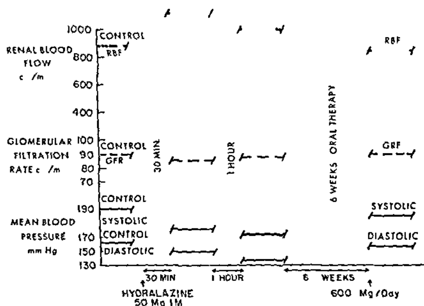


Fig 10 Renal hemodynamic response to hydralazine Although there is a moderate increase in renal blood flow following the parenteral administration of hydralazine this effect is only temporary and the renal blood flow returns to the control values after two to three hours despite the maintained reduction in mean blood pressure With continuous administration of hydralazine for a prolonged period of time there is no effect on renal blood flow Even when renal blood flow is up there is no increase in glomerular filtration rate during the acute response if anything there is a slight reduction in this modality

make hydralazine an ideal drug I think that this response is of practically no therapeutic value First of all the glomerular filtration rate does not change or may actually decrease as the renal blood flow goes up Certainly this does not help renal function Secondly the increase in blood flow is a transient effect lasting only several hours after the administration of single doses initially and this evanescent response to single doses lasts no more than three or four weeks with continued administration (Fig 10)

Dr Freis There are a few more points about the pharmacology Dr Schroeder that also bother me as to whether hydralazine is a peripheral

vasodilator entirely It is quite different in its action from nitrites in that nitrites produce diminution in central venous pressure and cardiac output whereas hydralazine seems to do the opposite And the other point is that this agent has a certain amount of selectivity of the vascular beds which are dilated Digital blood flow i e skin blood flow in the digit does not increase very much if at all and neither does muscle blood flow whereas central blood flow splanchnic renal and coronary blood flow do increase very markedly I wonder whether you might agree that there is a certain selectivity about this agent and that it isn t completely a nonspecific peripheral dilator

Dr Schroeder Of course I don t think we can assume that all blood vessels are constricted to the same degree in all areas of the body at any one moment We know they re not But I believe that Wilkinson Backman and Hecht found there was a digital blood flow increase furthermore there was not only that but if the material was injected into the femoral artery it increased only on that side The skin temperature went up on that side If you start at the basis of action of the stuff I think you are forced to the conclusion that its action is on muscle rather than on nerve

Dr Moyer One other thing bothers me about the data you presented Dr Schroeder and that is that you indicated that hydralazine is a monamine oxidase stimulator How do you interpret the stimulant effect? A monamine oxidase stimulator should destroy epinephrine more rapidly yet the effect that you get on cardiac output and the effect on the heart muscle by hydralazine is an epinephrine like response is it not?

Dr Schroeder That s right It s a cardio accelerator response and I don t know whether that s epinephrine or not We do know that many sympatholytic agents and antiepinephrine agents do produce tachycardia in man when they are given don t we?

Dr. Moyer But the output goes down under these circumstances and with hydralazine the cardiac output increases as much as 100 per cent

Dr Schroeder In normal patients

Dr Moyer And in hypertensives I believe that is what Hecht and his associates found

Dr Schroeder Fifteen per cent up in hypertensives and I think 58 per cent up in normals something like that

Dr Paton May I make one more point? The action of hydralazine has always seemed to me puzzling and I have looked at it myself although I am afraid I haven t published the data I found one action which Dr Schroeder didn t mention and I think it may be important—that of histamine release It is quite distinct from the antihistaminase action The whole group of histamine liberating compounds are actually those that show one of the things you thought was unique about hydralazine the so-called all or none effect They stop having any further action as soon as you have mobilized the amount of histamine that can be mobilized by that dose Of course these

drugs characteristically produce headache and they have a peripheral dilator mechanism I feel that there is a component of hydralazine s action which involves histamine release but of course it s so mixed that it s rather difficult to disentangle

DR SCHROEDER I agree with Dr Paton on that As a matter of fact when we give it to patients for the first time it looks as though the patients have got too much histamine in them and they even get a flu like syndrome with pains in the back and stuffy nose and so on Their rings get tight they have edema without weight gain their eyes are puffy they flush and many things happen that suggest histamine release But to my knowledge histamine is a vasoconstrictor isn t it?

DR PATON That depends enormously on the person

The Pharmacology of Ganglion Blocking Agents

W D M PATON

Royal College of Surgeons England

THE ACTIONS OF HEXAMETHONIUM AND PENTOLINIUM

It is hardly necessary to describe in detail the experiments on which our views of the action of drugs like hexamethonium and pentolinium are based It is generally agreed that drugs of this type act simply by an ability to compete with acetylcholine at the cholinergic synapse of autonomic ganglia They are themselves unable to excite the ganglion but if the synapse is active they reduce the efficiency of the transmission Since the antagonism is competitive the intensity of the block i e the proportion of cells for which synaptic transmission fails steadily increases as the concentration of hexamethonium or pentolinium in the extracellular space of the ganglion increases in relation to the acetylcholine released This type of action can be extraordinarily selective For practical purposes ganglia only are affected and the response of peripheral effector organs to stimulants is unimpaired Because these are quaternary salts they must exist in solution as ions that is they have to carry about a positive charge with them which greatly hinders their passage through cell walls This gives them the other properties not directly to do with ganglion block of being excluded from the central nervous system of being poorly absorbed by mouth of reaching a concentration in the plasma such as is to be expected if they lead an extracellular life and of being filtered by the kidney neither being reabsorbed nor actively secreted All this makes a tolerably coherent picture The specificity found for these drugs in the laboratory has been fully justified in clinical

practice so much so that no effect achieved by them should be interpreted in terms other than those of ganglion block From time to time peculiar reactions are observed and then additional properties are proposed on the heart on skeletal muscle or centrally but if on the one hand one fully appreciates the pharmacologic evidence and on the other one views such reactions critically I doubt that it is ever necessary to be driven to any other than ganglionic considerations even when discussing such obscure problems as the pulmonary changes occasionally seen in treated malignant hypertension[11]

THE PROPERTIES OF MECAMYLAMINE AND PEMPIDINE

The position is somewhat different when one turns to the newer ganglion blocking agents of which mecamylamine and pempidine are of greatest interest at the moment Mecamylamine is a secondary amine and pempidine a tertiary amine They are alike in their dissociation constants and not widely dissimilar in molecular weights The fact that they can exist although only to a small degree in the un ionized form transforms their characteristics[1,4,6,9,14,19]

1 As is well known they are active by mouth because they are for practical purposes completely absorbed For accuracy's sake perhaps one should say that the absorption may not be strictly complete but certainly 50 per cent or better This probably compares well with any other medicament given by mouth and means that even if absorption varies the proportion of the intended dose taken in cannot vary by more than a factor of two and normally will vary much less

2 At the same time their fate in the body is much modified by their intracellular passage for it is clear that many tissues especially spleen liver and lung and other tissues rich in nuclei can take up mecamylamine and pempidine

3 Thirdly the renal handling of these compounds is changed One might have wondered whether they would be treated like tetraethylammonium by being actively secreted by the tubules It emerges on the contrary that the un ionized form of these compounds is reabsorbed from the tubules The rate of reabsorption of course depends on the amount un ionized hence the greater excretion when the urine is acid and the greater reabsorption when the urine is alkaline This has offered the rather attractive idea of controlling duration of action by controlling the pH of the urine However other factors controlling duration of action which do not depend on urinary pH are also very important so that the scope for control in this way is somewhat limited The practical significance perhaps, is rather that under conditions when the urinary pH may change variations in apparent potency or in duration of action of these drugs must be anticipated

4 Lastly with mecamylamine and pempidine the possibility of central actions must be canvassed There does not appear to have been much analytic work on this aspect and indeed it would not be a very easy study But it is sufficiently clear from the clinical reports that mecamylamine at least can have central effects leading to confusional states tremor mania and the like

PROBLEM OF THE MECHANISM OF ACTION OF NONQUATERNARY GANGLION BLOCKING AGENTS

The differences between mecamylamine and pempidine on the one hand and hexamethonium and pentolinium on the other have been discussed so far as though they were purely pharmacodynamic I suspect myself that this is true for practical purposes But deeper differences of mechanism of action have been suggested, and the bases for this suggestion are worth examining

1 Slowness of Action. One of the remarkable features of mecamylamine is that it has an action lasting many hours Taking this with its known entry into and accumulation in cells [14] the deduction that the latter causes the former is nearly irresistible Further if entry into cells is so important for time-course action may it not also mean a different mechanism of action? Two comments must be made however The first is that for another group of drugs the barbiturates tissue take up (in their case by fat) is convincingly used to explain the brevity of action of drugs such as thiopentone it being supposed that fat storage rapidly lowers plasma levels and that the thiopentone later slowly released from the stores never reaches anesthetic levels in the plasma I see no reason why a different situation should exist for mecamylamine Indeed the more a tissue concentrates mecamylamine the lower will have to be the plasma level at which it is released again and hence the less the chance that during its release effective plasma levels will be achieved. Of course if mecamylamine produces a picture resembling ganglion block by combining intracellularly with nucleoprotein then this tissue concentration theory of prolonged action is eminently reasonable But this one could not accept The incidence of action by no means parallels distribution spleen kidney lung and liver take up the most mecamylamine up to 30 / plasma level brain (as a sample of nervous tissue) only concentrates 8-fold We can point, too to substances concentrated in a similar way but to a far greater extent without significant ganglionic action notably mepacrine One could also remark that *any* drug active by mouth (and therefore able to penetrate cells) is liable to enter the tissues of the body yet we do not attribute the extraordinary diversity of pharmacologic action among them to this single intracellular cause

A second comment is that intracellular tissue binding is not *necessary* for prolonged action We know of several quaternary salts whose relative inactivity by mouth points to a failure of cell-entry whose action is of comparable duration to that of mecamylamine—such as chlorisondamine pentacynium (Presidal) and its relative 159c56 and compounds such as IN 391 [1 1] If therefore prolonged action can occur *without* intracellular binding may not the association between the two be for mecamylamine and pempidine pure coincidence? Nor can we assume that compounds able to enter cells have necessarily prolonged actions for some nonquaternary analogues of hexamethonium have similar durations of effect*

At this point perhaps one ought to discuss what models for prolonged action the pharmacologist possesses By conventional drug theory one supposes that the onset and offset of action are dictated by two processes the rate at which the drug combines (associates) with its receptors and the rate at which it dissociates again If the ratio between association and dis

sociation speeds is high then the action of the drug is prolonged since that amount combined takes a long time to get away if the ratio is low then the reverse But there is another less obvious prediction If dissociation is relatively very slow then the time taken to reach maximum action is also prolonged Perhaps a domestic example may serve to illustrate this suppose you turn on the taps (faucets) of a bath and the drain away is closed then the bath will go on filling indefinitely *In other words if dissociation doesn't* occur at all association will continue indefinitely (until limited by saturation) On the other hand if the drain away is both open and very large equilibrium (with a virtually empty bath) is rapidly reached, here dissociation is rapid compared to association Between these limits the faster the rate of filling (association) of the bath (receptor area) compared to the rate of draining (dissociation) the longer it will take to reach any given approximation to the equilibrium state

I have found this a generalization of rather wide application when one studies for instance muscle relaxants atropinic substances antihistamines and so on For ganglion blocking agents too it *seems enlightening* Take the series of drugs TEA hexamethonium pentolinium pempidine and mecamylamine with durations of action ranging roughly from 30 minutes to 24 hours As far as I can judge from the published data the *shapes* of the time action curves are all alike differing only in scale and roughly speaking the time of maximum action is about one sixth of the total duration This is just what one would expect if the action of these drugs were dictated simply by the constants of association and dissociation One may notice too that if say the difference in time course between mecamylamine and pentolinium makes one propose a different mode of action between the two then the greater proportionate difference between pentolinium and TEA requires the same conclusion and we multiply modes of action to an extent that one cannot accept

One last point in this connection If what I have argued is correct then although there may be widely varying differences in time of peak effect, all the blocking agents should show some effect quite early This indeed seems to be the case There is no hint of any irreducible delay with any of these agents such as might point to the intervention say of a biochemical conversion or to the poisoning of an enzyme to some critical level

One may say therefore that the varying durations of action of ganglion blocking agents need point to nothing more than varying affinities for the receptor groups But surely uptake into the tissues must influence time course somehow? My own guess is that this is true but that the effect is *different from that normally supposed* and that *if you could prevent the* tissue uptake (other factors remaining the same) duration of action and potency would be increased At this point it could be retorted that pempidine is taken up less than mecamylamine by the tissues yet its duration of action is shorter not longer One can answer besides referring to the long acting quaternary agents by another pharmacodynamic suggestion It may well be that among compounds able to penetrate cells those that can do it best may also tend to be bound to the receptor area best In that case the association with nonquaternary salts of prolonged action and tissue take up may be a coincidence of the type which might lead one to suggest for instance that poliomyelitis is caused by the internal combustion engine The association between the latter rests of course on the common connection

between them in civilized life So too the prolonged action of a nonquaternary blocking agent and its tissue take up may both flow independently from a special physiochemical property of the molecule

2 Comparison of Clinical and Ganglion Blocking Potency A second reason advanced for supposing mecamylamine to operate in a different manner from hexamethonium arises by comparing doses effective in man with those effective in blocking ganglia in animals It is undoubtedly noticeable that whereas say mecamylamine and hexamethonium differ only slightly in potency as judged say by the dose required to produce 50 per cent block of a ganglionic response the clinical dosage required per day (comparing parenteral hexamethonium with oral mecamylamine) is proportionately much higher for hexamethonium But such a comparison is extraordinarily hazardous with agents of different durations of effect Suppose that mecamylamine has an action eight times as long as hexamethonium For comparable effects hexamethonium would need to be given eight times as often for a dosage of mecamylamine twice a day this implies a dose of hexamethonium every one and one half hours Obviously this will never be done but a rather large and correspondingly wasteful dose of hexamethonium will be given less often Under such circumstances one can readily appreciate that the briefer acting drug will appear proportionately less effective

In short one suspects that while the laboratory investigation may compare intensities of block, clinical comparisons rest on the product of intensity with duration of action

3 Differences in Type of Blocking Action on Ganglia The very interesting statement has been made that the response of a ganglion partly blocked by mecamylamine does not fade with continued excitation at a fairly rapid rate (10 shocks/second) as it does with hexamethonium [3] This could be a very important difference both for mechanism and for use since as will be argued later the special sensitivity of a partly paralyzed ganglion to rapid or sustained excitation may be a valuable feature clinically However Corne and Edge[4] have not been able to demonstrate this difference and my own experiments have failed to reveal it I have no explanation for the divergence of my results from those of my esteemed collaborator Professor Zaimis and her colleagues It is such things that make pharmacology interesting

4 The Other Actions Possessed by Nonquaternary Ganglion Blocking Agents A fourth reason for questioning whether the nonquaternary blocking agents act in the same way as hexamethonium arises from considering the effects on synapses or tissues other than ganglionic [3, 4] It is clear that mecamylamine and pempidine can depress the heart beat (mecamylamine more than pempidine) and can depress the response of smooth muscle to the usual stimulants Pempidine is reported to display occasionally a stimulant effect on the ileum and to have in large doses a pressor action recalling, but not altogether similar in properties to that seen with TEA Mecamylamine has some vasodilator action on a dog s perfused leg [4] But none of these effects seem likely to be significant in practice

Two actions may however be more significant First neuromuscular effects Both mecamylamine and pempidine can in large doses produce neuromuscular block In smaller dosage they potentiate d tubocurarine and antagonize decamethonium and suxamethonium Thus far they are like the quaternary ganglion blocking agents But Dr Zaimis and her colleagues also

describe an ability of mecamylamine *to change* the type of action of dec-amethonium and suxamethonium so that the block they produce becomes for instance neostigmine reversible[3] One can indeed observe something of this sort sometimes with d tubocurarine or hexamethonium but less striking There certainly is something fishy about mecamylamine one s uncertainty arises from wondering how far its peculiarity depends on its prolonged action which as already stressed makes it very hard to compare with briefer drugs For our present purpose the question is What does this imply for the ganglionic synapse? Knowing what we now know of the extent to which ganglionic and neuromuscular actions can be dissociated one must say that it *may* imply nothing and it is in such a position of suspended opin ion waiting on further analysis that perhaps the problem should be left

The second action by mecamylamine also reported by Dr Zaimis and her colleagues is that of a local anesthetic potency comparable with that of procaine and although it does not appear to have been explicitly tested the same is doubtless true for pempidine To interpret this perhaps some work by J W Thompson and myself[17] on the synergism of procaine amide with hexamethonium is relevant since procaine amide also possesses a local anes thetic action comparable with that of procaine but it is far more stable It has a fairly prolonged action on a ganglion antagonizing both the action of acetylcholine *when it is released or injected and the release itself by the* nerve endings When combined with hexamethonium the block achieved is greater than purely additive suggesting that to combine competitive block with a modest antagonism to acetylcholine release is one way of achieving a truly *potentiated* effect In the light of such results one wonders whether *such a local anesthetic effect may not augment the ganglionic action of these* nonquaternary amines Certainly it could readily explain the rather modest reduction in acetylcholine output by a perfused ganglion seen for pempidine (in a large dose) by Corne and Edge[4] and for mecamylamine by myself This reduction is certainly inadequate itself to cause block but it might have some adjuvant influence It is less certain whether for a human dose say of 1 mg/kg this type of action is significant for Thompson and I found that it needed more like 15 mg/kg of procaine amide by the intravenous route to exert useful ganglionic effects There is however something suggestive in all this and it would be interesting to examine the behavior of other simi lar compounds with a rather greater local anesthetic activity

5 Action on Acetylcholine Synthesis The last suggestion to consider about the action of mecamylamine and pempidine is that they can interfere with acetylcholine synthesis Although this could not explain their ability to antagonize for instance nicotine it is a pertinent suggestion since any drug related to acetylcholine in one respect is liable to exhibit other relationships Dr J E Gardiner in my laboratory following his study of the hemicho-liniums has tested pempidine in this respect He finds however that at concentrations of 10^{-4} and 10^{-3} molar pempidine does not reduce acetyl choline synthesis by brain homogenates nor by brain mitochondria (which contain the choline acetylase) whether the mitochondria are intact or broken This means two things pempidine *does not interfere* with the transport of choline into the cell or mitochondrion as the hemicholiniums do nor does it block the intracellular choline acetylase

6 Summary of Mechanism of Action There is no decisive evidence that mecamylamine and pempidine block ganglia in any way different from

hexamethonium pentolinium or the long acting quaternary salts It is perhaps worth mentioning that although mecamylamine and pempidine are not quaternary they are both such strong bases that over 99 per cent of the amount circulating or in tissue spaces will be in the ionized form comparable with a quaternary salt There is however a suspicion that some other factor *may* contribute for which a feeble local anesthetic effect is a special candidate Their prolonged action like that of the long acting quaternary compounds can be attributed simply to receptor affinity and it is significant that the shape of the action time curve is similar with all ganglion blocking agents after making due correction for time scale

THE POTENTIATION OF GANGLION BLOCK BY DIURETICS

Before leaving pharmacologic matters mention should be made of the finding that two diuretics acetazoleamide and chlorothiazide can increase considerably the activity of ganglion blocking agents [9 10 13 14 0] This promises to be a fairly straightforward story First both drugs tend to alkalize the urine acetazoleamide the more strongly in line with its stronger and more selective inhibition of carbonic anhydrase Such alkalinization will as mentioned earlier increase reabsorption of the nonquaternary ganglion blocking amines in fact a delayed excretion under these conditions has been demonstrated This type of potentiation however could affect only blocking agents which can exist in un ionized form The second feature is that both diuretics but especially chlorothiazide increase sodium output and diminish extracellular fluid It was reported quite early in the clinical reports on ganglion block that low sodium diets sensitized to the blocking drug and it seems reasonable to suppose that the same phenomenon is appearing in another form One could envisage that sodium loss itself in some way brings this effect about but it is more attractive and so far I think permissible to attribute it to the net loss of fluid leading to a susceptibility to block comparable with that achieved for instance by a small hemorrhage The only difficulty in this is the observation by Tapia *et al* [0] that venous occlusion of three limbs during the administration of chlorothiazide does not have a significantly more pronounced effect than usual as one might expect but more work will no doubt clarify the position The influence of sodium and water loss will of course extend also to quaternary blocking agents and a potentiation of these as well as of mecamylamine by chlorothiazide has been described

The possibility of sustained chlorothiazide administration with the object of reducing the dose of ganglion blocking drug immediately presents itself This seems primarily a clinical problem in balancing advantages of dose on one side against dangers of electrolyte depletion sensitization to the diuretic and the like on the other Perhaps one pharmacologist may be allowed to remark that for his taste despite a vested interest in drugs the fewer that are used the better

SOURCES OF VARIATION IN THE RESPONSE TO GANGLION BLOCK

Although there is no especially new work on the sources of variation in response to ganglion block, no discussion of the action of these drugs can

be complete without some allusion to it for it is one of the rather characteristic features of their use that patients require individual "titration" in assessment of their needs There are three main ganglionic causes for such variation the pattern of autonomic activity in an individual the sensitization of ganglia by intense or prolonged excitation and the varying susceptibility of different ganglia

Ganglion block like neuromuscular block can reveal itself only if there is activity down an autonomic pathway If a channel is inactive the existence of block is only potential and not explicit One would expect therefore that with the use of drugs one could even determine the autonomic activity normally present in the body by comparing the physiologic state of a man before and after block This has some relevance to the notion that individuals can be classified as for instance vagotonic or sympatheticotonic If this classification were true one would expect to find individuals grouping themselves after block with either a selective parasympathetic or a selective sympathetic loss of function This was a point that Dr Steinberg and I took up in the practical pharmacology class at U C H from 1951 to 1954[15] In a group of students one volunteer received 25 mg hexamethonium bromide *subcutaneously the others subjected him to a systematic series of tests* before and after the drug on supine and standing blood pressures and pulse rates skin temperature body temperature salivary secretion ocular accommodation of lens to distance and pupils to light and of sweat rate We then scored each subject as to whether a significant effect on various autonomic functions had been produced The striking result was that no two subjects in this fairly homogeneous population of over 40 healthy young students gave the same pattern of response It seemed indeed that there was no great division into two main groups but that every subject possessed his own autonomic fingerprint" as we termed it In a way this is obviously to be expected for the autonomic carries the expression of our personalities as well as a number of homoiostatic processes and if personalities differ as they do so should their bodily expression

There is however another process which picks out active autonomic pathways this is what can be termed an enhanced fatigability of the partly blocked synapse[16] With a normal ganglion increasing rates of excitation up to about 20/sec yield increasing effector responses this state of affairs is obviously a major requirement for the economy of the body if autonomic reflexes are going to help in responding to say posture or hemorrhage But after partial block the ganglion becomes proportionately much more sensitive to the higher rates of excitation and to continued as opposed to brief excitation The results of this are first that a short period of test stimulation may give a gross underestimate of the degree of block of sustained autonomic activity secondly that an acceleration of autonomic discharge rate normally producing an increased response may now produce a much smaller one so that vigorous autonomic reflexes may be especially hard hit and thirdly, that among the various autonomic activities in the body the most active will be picked out for deeper block and the slower paced ones may be less influenced It is to this mechanism that one can turn to account for the persistence of postural hypotension even when supine blood pressure is little different from normal or for the extraordinary sensitivity to block of some patients or for the resistance of some phasic autonomic reflex to block when tonic responses are clearly reduced

The third source of variation is that different ganglion cells though exposed to the same concentration of blocking agent may be blocked to varying degrees [16] This observation is as old as J N Langley s experiments with nicotine was repeated when Eccles studied ganglion action potentials and has been repeatedly confirmed with later blocking agents We have little certain explanation for it, although the known variations in ganglion cell structure and size and in preganglionic conduction velocities allow one to suppose that ganglionic synapses form a fairly widely distributed population with a significant variance in acetylcholine release disposal and response For the accessory ganglia lodged in spinal nerves and rami communicantes an inaccessibility to the drug may also be important

One synapse may be mentioned here that between the splanchnic nerve and the suprarenal medulla, which has the properties of an autonomic ganglion Most investigators including myself have found that it is rather resistant to ganglion blocking agents as tested by the pressor response to brief periods of repetitive stimulation It is however a good deal more readily paralyzed when it is in a state of continued activity This came out during some recent experiments on hemorrhagic shock in which I used the method described by my colleague J R Vane [1] for testing the presence of sympathetic amines in blood A suitable strip of isolated tissue (rat s fundus strip) is superfused with blood from an artery the blood being returned by a vein the preparation has considerable tone and a small dose of Adrenalin or splanchnic nerve stimulation relaxes it The method thus gives a continuous record of active substances in the blood If now an animal is bled, the strip relaxes and stays relaxed as long as the hypotension persists implying a sustained splanchnic suprarenal activity If now a dose of hexamethonium is given the relaxation disappears promptly and completely almost as though a tap supplying catechol amines had been turned off Evidently as with other synapses tonic activity especially of a vigorous kind is more sensitive to block than phasic responses No doubt in the responses of patients to ganglion block a temporary activation of the splanchnics previously quiescent would also break through although a sustained activity would be paralyzed

THE RELATION OF CHEMICAL STRUCTURE TO PHARMACOLOGIC ACTION

The connection of chemical structure with action is perhaps a topic that pharmacologists should discuss only among themselves But the extraordinary properties of the methonium compounds and the more recent shock provided by mecamylamine have made this a subject of fairly general interest I would like to describe briefly some recent work by E W Gill and H R Ing [8] which has introduced some entirely new ideas They seized on the odd fact that although hexamethonium blocks the terminal groups it possesses are alone powerful ganglion stimulants They pointed out that it seems only to be compounds with so to speak stimulant ends that are very sensitive to chain length By contrast bistriethylammonium derivatives change activity much less as the distance between the groups shortens or expands Gill and Ing then formulated the hypothesis that, when hexamethonium acts each end forms a union which would ordinarily excite the cell surface that excitation normally involves some change in configuration

of the surface and that the reason hexamethonium does not excite is that this double combination "locks" the excitable surface so that the normal changes in permeability cannot take place hence hexamethonium paralyzes despite the stimulant character of its terminal groups

Gill and Ing have supported this with some new calculations made possible by a recent advance in knowledge about the rotations of these chains of the distance between the active groups yielding a series of distribution curves of length against frequency If they then suppose that activity depends on the proportion of molecules whose stimulant ends are between 4 5 and 6 0 A apart, they are able to predict in a really remarkable way the ganglionic activity not only of the range of methonium compounds but of many other series too

Two other consequences follow The first is of course that one could not assume that the receptors to which these compounds are attached are all spaced *exactly* the same distance apart rather one would expect a fairly narrow range of distances If then one had an absolutely rigid molecule even with its ends correctly distanced it should be of low activity because it can combine only with a small proportion of the receptor pairs This in fact, Gill and Ing verified Thus one needs for this type of action some flexibility in the molecule

The second prediction tested by Gill and Ing was that by making a molecule partly rigid partly flexible they should be able to arrange that the majority of its possible configurations are within the relevant range This too they were able to establish

The theory of Gill and Ing applies of course primarily to structures with two active groups It supports the old naive idea that Dr Zaimis and I expressed in our original paper that the distance between the active groups was an estimate of inter receptor distance on the ganglion cell membrane But the significance of the work lies I think in the remarkable quantitative agreements which suggest that a real insight into the nature of the receptor membrane has been achieved Although with structures like mecamylamine we move away from the compounds studied by Gill and Ing I have no doubt that a physicochemical approach of comparable skill in other fields would prove equally rewarding

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Pharmacology of Adrenergic Blockade in Hypertension

CARROLL A HANDLEY

Baylor University College of Medicine

Although the etiology of essential and malignant hypertension is still unknown the importance of the sympathetic nervous system in maintaining the condition is generally accepted Reports over the past years have shown a measurable degree of relief from surgical sympathectomy The advent of potent adrenergic blocking agents a few years ago engendered the hope that these drugs might be useful in the treatment of hypertension by producing "chemical sympathectomy"

The use of members of the Fourneau series of adrenergic blocking agents in essential hypertension actually causes a rise in resting blood pressure This effect of these compounds is undoubtedly due to a central stimulant action and unrelated to adrenergic blockade Clinical treatment of hypertension with the more effective adrenergic blocking agents has also produced variable results but favorable results have been obtained with the B halo alkylamines in all degrees of hypertension

It has been definitely established that vasomotor reflexes are still highly active in the presence of essential and malignant hypertension The kidney is very responsive to vasoconstrictor impulses and to circulating norepinephrine Inhibition of sympathetic vasoconstrictor tone by high spinal anesthesia has been shown to produce an increase in renal blood flow in both human essential hypertension and experimental hypertension in dogs Phenoxybenzamine (Dibenzyline) is highly effective in preventing reflex renal vasoconstriction and renal vasoconstriction from epinephrine or norepinephrine This can readily be demonstrated by injecting Dibenzyline into one renal artery of a dog and infusing ephinephrine or norepinephrine intravenously or by causing reflex vasoconstriction by bleeding Any of these procedures will cause vasoconstriction and a reduction of renal blood flow on the uninjected side while the renal blood continues at approximately the control rate in the kidney with adrenergic blockade The role of renal vasoconstriction if any in the development and maintenance of essential and malignant hypertension has not been determined Adrenergic blocking agents are however able to prevent renal vasoconstriction most effectively Actually the primary effect of adrenergic blockade in reducing the blood pressure in hypertension is by preventing the compensatory vasoconstriction that occurs on assuming the upright position

The use of adrenergic blocking agents in the treatment of hypertension has been disappointing because of the numerous side effects Particularly annoying are dizziness due to reduced cerebral blood flow and tachycardia on assuming the upright position

Development of tolerance to the hypotensive action of adrenergic blocking agents is a characteristic finding This is analogous to the gradual rise in blood pressure seen after surgical sympathectomy

Discussion

JOSEPH R DIPALMA *Moderator*

BENEDICT ABREU	SIBLEY HOOBLER
RALPH FORD	EDWARD MEILMAN
EDWARD FREIS	JOHN MOYER
STANLEY GITLOW	WILLIAM PATON
ARTHUR GROLLMAN	H MITCHELL PERRY
CARROLL HANDLEY	ALBERT PLUMMER
WILLIAM HOLLANDER	HENRY SCHROEDER

DR DIPALMA There are certain interesting problems concerning the pharmacologic activity of the last group of drugs that we've discussed One is the problem of just how the blood pressure is lowered with ganglionic blocking agents Is this Dr Paton primarily due to a reduction in cardiac

output or is it primarily due to a vasodilatation or is it a combination of both?

Dr Paton I think perhaps I may not be the best person to answer this because I haven't done much on cardiac output myself But from my own experience and from the literature I have little doubt that the primary effect is on arteriolar tone but of course if you reduce arteriolar tone and perhaps venomotor tone as well this may easily end up in a reduction of venous return to the heart and hence all this follows I find that in these discussions one very quickly gets into the hen and egg difficulty as to which produced which But if I have to choose I certainly go for arteriolar tone

Dr DiPalma Do any other members of the panel wish to comment on this?

Dr Grollman I think the change in cardiac output in most of these cases is secondary but you can't actually dissociate the two I think this sort of phenomenon is represented very nicely by the effect of the nitrite ion We're used to thinking of the effect of nitrite as being depressor because the earlier experiments were done on laboratory animals usually with the chest open or at least anesthetized In the intact man nitrites actually will not lower the blood pressure in the supine position despite vasodilatation because there is a response of an increased cardiac output maintaining normal blood pressure Only when the dose is increased to the point where venous return is insufficient to maintain the increased cardiac output do you get a drop in blood pressure The same thing applies clinically with the ganglionic blocking agents

Dr Hoobler I should like to make a comment on the previous points Any measurement that's been made of cardiac output in a human being in the recumbent position or the upright position with a ganglion blocking agent has shown a decrease in cardiac output There is essentially no change in peripheral vascular resistance (TPR) Furthermore with the exception of the hands and feet, where there is unquestionably enormous arteriolar dilatation I know of no area of the body where there has been any increase in blood flow over and above what might just match the change in blood pressure I would put the sequence of events as follows First a decline in venous tone occurs which would naturally decrease venous return to the heart Second a decline in cardiac accelerator tone or cardiotonic activity occurs Third a decrease in arteriolar tone follows I'm sure they are all part of the one package because I think these things act everywhere and you can't strike out certain segments But in the human patient with hypertension I think this is the order of action

Dr Moyer I agree with Dr Paton and Dr Grollman in that the initial response is vasodilatation The interpretation of the sequence of events will depend largely on the method used to determine cardiac output Were one to use the Fick method measuring cardiac output before the drug was given and then again 10 to 30 minutes after drug administration one would draw the conclusions that Dr Hoobler has just drawn However if one used a method so that cardiac output can be determined from minute to minute after the

parenteral administration of hexamethonium one would come to a different set of conclusions Figures 1 and 2 are two experiments In Figure 1 it is quite apparent that the initial *response was vasodilatation with a reduction in* peripheral resistance Actually there was a slight initial increase in cardiac output However within 10 minutes cardiac output decreased apparently because of a reduction in venomotor tone and consequently a decrease in venous return

The subject in Figure 2 was a dog which had bradycardia due to morphine anesthesia When the ganglionic blocking agent was given there was a sharp increase in pulse rate associated with a temporary increase in cardiac

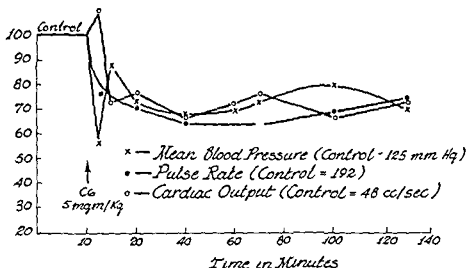


Fig 1 Cardiovascular response to hexamethonium administered parenterally An initial slight increase in cardiac output is associated with a sharp reduction in peripheral resistance However this is followed shortly by a decrease in cardiac output due apparently to a reduced venous return as venomotor tone is depressed Twenty to 30 minutes after the administration of the hexamethonium both cardiac output and mean blood pressure are decreased with little alteration in the calculated peripheral resistance

output at the same time that the blood pressure went down This combination of effects could only mean that peripheral resistance had decreased following the administration of hexamethonium However here too cardiac output decreased despite the increase in pulse rate This should mean that venous return had fallen off as ganglionic blockade was established I can only conclude from these observations that the primary effect is reduced sympathetic tone expressed first by decreased arteriolar resistance and later by reduced venomotor tone and its associated reduction in venous return to the heart When calculated some 20 or 30 minutes later at a time when the cardiac output and blood pressure are both reduced I have serious doubts as to the validity of peripheral resistance having any significance as to how things got that way

DR DIPALMA Now there is another question here which is pretty much along the same line and perhaps it can be settled at this time Is there any evidence that ganglionic blocking agents used clinically can produce block on the afferent side?

DR PATON I could certainly quote the evidence that there isn t This question has been present ever since the time that people found acetyl choline could stimulate certain sensory endings People have wondered whether this involved a central peripheral cholinergic sensory synapse I m not really aware of any good evidence that ganglion block does anything to any physiologic sensory pathway

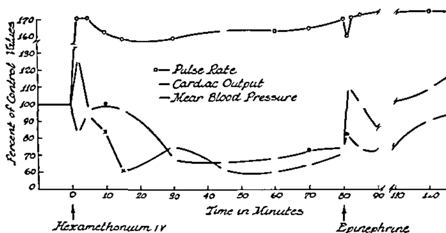


Fig 2 The cardiovascular response to the administration of hexamethonium in a dog hich had previously been anesthetized with morphine and phenobarbital As a result of the morphine administration bradycardia was rather marked prior to the administration of hexamethonium When hexamethonium was given there was a sharp increase in pulse rate due to ganglionic blockade and release of the vagal tone Here again the initial effect was a reduction in peripheral resistance followed by a decrease in both cardiac output and mean blood pressure so that calculated peripheral resistance was not altered by comparison to the control value However the information that this calculated peripheral resistance conveys is questionable (From J Pharmacol & Exper Therap 106 157 195_)

DR HOOBLER May I ask Dr Paton a question in this regard? When I was in Switzerland, Dr Bein showed me some work on the Ciba drug Pendiamide which by action transpotentials appeared to produce afferent stimulation This is the only evidence that I know of any ganglionic blockade I wonder if you d like to evaluate it?

DR PATON I think that this was afferent from the splanchnic area wasn t it?

DR HOOBLER Yes that s correct

DR PATON Of course this is a little difficult because the splanchnic area

is recording what s happening in a bed full of ganglia The wall of the gut is full of little synapses sensitive to the ganglionic blocking agent And I should have thought that it would be a very difficult thing to check what the ganglionic blocking agent might appear to be initiating in this type of activity and so change the incoming signal but I wouldn t have thought this was decisive enough to prove the point

Dr DiPalma Another problem has developed with respect to ganglion blocking agents It has been observed by many people that the administration of chlorothiazide or low sodium diet seems to enhance the effect of the ganglionic blocking agent Is there a good explanation for this other than the obvious one that the blood volume is perhaps less? Dr Freis can you answer that for us?

Dr Freis I think the obvious one is a pretty good answer Certainly you can see after you ve produced sympathetic inhibition with the ganglion blocking agent a marked sensitivity to minor degrees of blood loss As little as 50 to 100 cc removal of blood will produce some reduction of blood pressure which is something you don t see in the absence of sympathetic blockade I think the reason for this is that ordinarily the baroreceptors go into action and we have not only arterial constriction with minor degrees of blood loss and reduction in cardiac output but we also have postarteriolar constriction which tends to squeeze blood back into the central veins

Dr DiPalma Another question about the ganglionic blocking type of drug A peculiar type of pneumonitis has been reported with hexamethonium It goes under various terms First of all is this seen with other ganglionic blocking agents other than hexamethonium and also what is the possible mechanism?

Dr Perry I think Dr Paton may have more information than I do about this but in our experience we have never seen it with anything except hexamethonium I don t have any real ideas as to what the mechanism of action might be In our group of patients this particular syndrome was interestingly concentrated in a very small segment of our hypertensive population All the patients might be described as malignant hypertensives all were azotemic, most were Negroes and most were males But I don t know what to make of this I think Dr Paton may know something about this having occurred following some other ganglionic blocking agent

Dr Paton Again I have no direct experience with this There was an English report a few months ago in which the typical pneumonitis was seen in a patient who had taken pentolinium As to the mechanism I don t think anybody really knows With reference to the apparent specific effect of hexamethonium let us review its comparative pharmacology I can t believe that it has any other than its usual actions here It s not metabolized You can inject it in very large doses into animals It doesn t do anything to the lung in dogs My own theory is that the reason why pneumonitis is seen with hexamethonium is that hexamethonium controls blood pressure less smoothly than other ganglionic blocking agents Perhaps there is occasional adrenalemia during postural hypotension adrenalin having quite a toxic effect in the lung of some species

DR. FRIES I just wanted to corroborate Dr Perry's experience Ours has been exactly the same limited exclusively to hexamethonium

DR. MEHLMAN One year ago I saw a patient who had me quite excited because it was the first example I'd seen of this hexamethonium lung It was a woman who had severe hypertension and finally congestive failure with a low sodium syndrome and a high BUN She died in about 48 hours. On autopsy she had typical findings, but when we went through the entire record she had never received any ganglionic blocking drug at all, and this was carefully substantiated by contact with previous physicians who had taken care of her

DR. PERRY May I make a comment on this? Our pathologists have felt that this entity is not distinctive pathologically We feel we can distinguish it clinically but pathologically this entity cannot be separated from uremic pneumonia The patients in whom we described this fell into two entirely distinct categories. The first category of patients had never had nonprotein nitrogen levels in their blood higher than 60 mg per cent which is distinctly not uremic The other patients were patients who were uremic and I have always thought that when this was described in uremic patients this was really uremic pneumonia whereas in the other patients it has seemed to be something distinct

DR. DIPALMA Since mecamylamine is completely absorbed and it seems to be very effective why not use it in preference to any of the other ganglionic blocking agents?

DR. SCHROEDER With mecamylamine you can get a syndrome resembling delirium tremens Possibly this is due to the caffeine-like structure of mecamylamine This syndrome scares the doctor as well as the patient We have only seen it in the uremic or azotemic patient but it definitely has a central toxic action.

I want to say one thing about hexamethonium lung if I might We got the impression that this is always a fatal disease However one patient we observed had it twice The x-ray was typical as described in the original cases We treated her with hydrocortisone in large doses and she recovered. It was thought to be an inflammatory thing—at least it had some characteristics of the inflammatory reaction At any rate there was one with probable recovery

DR. DIPALMA Are there any other comments on this?

DR. HOLLANDER I would like to ask Dr Paton a question. Can you conceive of a ganglionic blocking agent which will not produce postural hypotension and interfere with the sympathetic readjustment of the blood pressure?

DR. PATON No I don't think so People will go on looking for it, which is something one should check on but I don't believe it will materialize

DR. PLUMMER I'd like to ask a question. Maybe Dr Paton would know

more about it It seems that I recall reading a few months ago an English report I think in the British Medical Journal that chlorothiazide delayed the excretion of mecamylamine clinically which might have something to do with this activity Do you recall that report Dr Paton?

DR PATON Yes and the authors attributed it to alkalinization of the urine Both chlorothiazide and Diamox do produce alkalinity This will delay the excretion of both tertiary and quaternary ganglion blocking agents

DR FORD If we can go back to that original subject in answer to your question on the advantage of mecamylamine I think there are two reasons that one should use mecamylamine in preference to other agents such as hexamethonium The first is that the duration is longer the average duration of hexamethonium in clinical use is four hours and the average duration of mecamylamine is roughly 12 but sometimes as long as 24 This contributes to a more stable consistent clinically efficacious program The second is that the absorption is 100 per cent with mecamylamine whereas with hexamethonium it is something like 5 or 10 per cent The doctor feels more secure if he knows that he is giving something that is absorbed Certainly its effect on the blood pressure will not be quite so erratic and attuned to the patient s bowel habits However balancing these out ganglion blockade is still ganglion blockade and if one used the titration procedure he could achieve just as good a response in the treatment of hypertension with either of these two compounds

DR DIPALMA Do adrenergic blocking agents give any information on the possible etiology of essential hypertension?

DR HANDLEY I don t know of any There should be no reason why they would give you any more information than the ganglionic blocking agents because actually they achieve very much the same thing

DR ABREU I would like to ask Dr Handley Why don t adrenergic blockers lower the normal blood pressure?

DR HANDLEY Oh I think they do decidedly

DR ABREU If given slowly they do not

DR FREIS We had a little experience with adrenergic blockade and perhaps it would be worth mentioning now There is an unimpressive reduction in the blood pressure in hypertensive individuals when Dibenzyline is infused intravenously to a point where there is practically no response to epinephrine There is vasodilatation in the periphery as measured plethysmographically which is comparable to ganglion blockade

There is one puzzle to me concerning Dibenzyline that I would like to throw back as a question This material is apparently irreversibly combining with receptor sites permanently blocking the effect of norepinephrine on receptors Why is tolerance so rapidly demonstrable in man? Does this also occur in the laboratory?

Dr Handley We have given these blocking agents over a period of many weeks and we don t see that type of tolerance develop I think that probably that type of tolerance is something related to the same thing you get with sympathectomy In sympathectomy in people with hypertension you get a gradual return of blood pressure toward the hypertensive level and I wonder if that s not the same type of thing which is seen with the adrenergic blocking agent In connection with lowering normal blood pressure it is more difficult with any type of agent that reduces blood pressure to lower a normotensive blood pressure than it is a hypertensive blood pressure The same was discussed this morning It is also relatively easy to raise the blood pressure from hypotensive levels but it is more difficult to raise it if the blood pressure is at the hypertensive level already

Dr Schroeder In answer to your question about whether they contribute to knowledge of etiology of hypertension I think they do I think they do *point out to us* at least with the adrenergic blocking agents that *something* else is keeping the blood pressure up Even in the case of ganglionic blocking agents clinically one cannot satisfy oneself that they are as effective as has been recorded if one keeps the patient in bed and measures enough blood pressures during the day Now of course if you measure the blood pressure standing, then I will agree that you get a postural hypotensive effect It looks awfully good on paper but if you keep the patient supine I think you will be rather disappointed You may get a moderately fluctuating effect but you certainly can t produce normotension or anything approximating it

It should also be pointed out that a rabbit aorta strip which has been subjected to Dibenamine does not respond to epinephrine It does contract under these circumstances when exposed to angiotonin and pherentasin

Dr. Ford I think that the beneficial effects of ganglionic blocking agents and adrenergic blocking agents in hypertension point closer to an etiologic concept You can expand this to say that the augmentation of the antihypertensive effects of these two groups by diuretic agents points us even closer to an etiologic concept.

Dr Freis I don t think that we can say just because the drug lowers the blood pressure of the hypertensive that it has any etiologic significance I think that s a trap We should carefully avoid that Furthermore the manner in which the ganglion blocking drugs and the adrenergic blocking agents appear to lower blood pressure does not look like the physiologic reversal of the pathologic process

Therapeutic Use of Hydralazine (Apresoline) and Rauwolfia Compounds in Hypertension

S. W. HOOBLER and PEDRO BLAQUIER
University of Michigan Medical School

It is a remarkable testimonial to advances in the drug treatment of hypertensive disease that in the brief span of one decade it has become no longer necessary to ask whether the blood pressure can be lowered by any reasonable treatment regimen. Rather we must now inquire what method of blood pressure reduction will produce minimum side effects and maximum benefit in terms of chronic management of the disease. As the number of available therapeutic agents multiplies, the criteria for the superiority of any regimen become more rigorous.

I have been asked to discuss reserpine and hydralazine, two unusually interesting drugs which were among the first to be introduced for the treatment of hypertension. The nature of their action is such as to make it extremely difficult to give a precise measure of their effectiveness. Moreover, we have never attempted a thoroughgoing clinical evaluation of either reserpine or hydralazine in the University of Michigan Hypertension Clinic. Certainly others could give you a more competent discussion. I will have to resort to the clinical impressions we have gained from working with these drugs in the past eight to ten years.

THERAPEUTIC USE OF RAUWOLFIA COMPOUNDS

No Rauwolfia derivative has been proved to be more effective in blood pressure reduction than the pure alkaloid reserpine, the action of which meets the four criteria of effectiveness listed in Table 1. When given paren-

TABLE 1. EFFECT OF RESERPINE IN HYPERTENSION

MODE OF ADMINISTRATION	DOSE	USUAL EFFECT ON MEAN BLOOD PRESSURE	
		MAGNITUDE	TIME OF ONSET
		mm Hg	
Single intravenous or intramuscular	2.5–5.0 mg	−40	30–60 min
Single oral	1–2.0 mg	−10	3–6 hrs
Continuous oral	1 mg daily	−20	1–8 weeks
Withdrawal effect		+20	1–8 weeks

terally the drug is especially effective in moderating an acute hypertensive crisis. Since an overdose will not precipitate acute shock, reserpine is useful when the blood pressure cannot be followed for a prolonged period as

when the patient is seen in the home We have not had any experience with a comparable oral dosage of the drug It is not easy to obtain proof that continued oral administration produces and maintains blood pressure reduction since it is always difficult to exclude the psychodynamic effect of the procedure of giving a new drug to a patient with hypertension It is our impression that 25 to 50 per cent of subjects with a moderate blood pressure elevation exhibit a continued mild depressor response This is supported by several careful double blind experiments [1] The drug is less effective in severe or malignant forms of the disease and should never be used in these cases as the sole antihypertensive agent since valuable time may be lost waiting for an effect which may never become evident

Withdrawal experiments in particular have convinced us that the drug is effective in many cases of mild hypertension After six to eight weeks of initial "reserpinization" with 0 75 to 1 0 mg daily it is possible to maintain therapeutic effects with doses of 0 125 to 0 25 mg daily at which level side

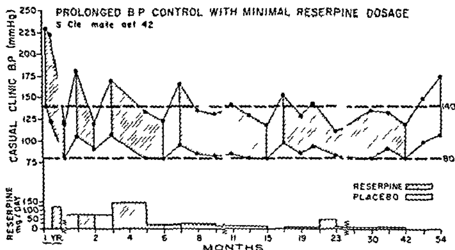


Fig 1 Effect of long term reserpine therapy in essential hypertension

effects are rarely apparent A sample of our experience is recorded in Figure 1 Sustained blood pressure reduction at so little inconvenience to the patient would seem to be worth while However it must be conceded that there is no proof that such treatment in mild forms of hypertensive disease favorably affects the mortality rate Because side effects are minimal and blood pressure reduction is continuous the method of first choice in the treatment of mild hypertension continues to be the administration of reserpine with or without chlorothiazide Empirically we have chosen a sustained blood pressure of 160/100 in a young person as the level at which such therapy is started we believe that this program should be instituted in the older labile hypertensive subject with repeated transient elevations of blood pressure exceeding 200/100

There is great variation in the response to Rauwolfia alkaloids About one half of the patients achieve worthwhile blood pressure reduction but many of these exhibit unusual reactions which require reduced dosage or omission of the drug from the treatment program Table 2 lists some of

TABLE 2 IMPORTANT SIDE EFFECTS OF RAUWOLFIA THERAPY

TYPE	FREQUENCY	EFFECT ON TREATMENT	REFERENCE
Depression	Occasional	Omit	3 4
Activation of gastrointestinal disease	Occasional	Omit	5
Weight gain	Frequent	Omit	6
Fluid retention	Occasional	Omit	7
Fatigue	Often	Reduce or omit	6
Premature ventric beats	Rare	Omit	8
Hypotension with anesthesia	Rare	Omit pre operatively	9

the more important side effects of treatment Fatigue apathy and depression may develop so slowly that they are not recognized as side effects until the drug is discontinued [10] Relief from these symptoms without loss of antihypertensive action may occasionally be achieved by reducing the total daily dosage When it is necessary to add more powerful drugs to the regimen in order to achieve sufficient blood pressure reduction reserpine is frequently discontinued since we believe that the side effects of ganglion blockade are bad enough without superimposing the Rauwolfia effect of fatigue and depression even if omitting such treatment results in a larger dose of ganglion blocking drug

From what has been said it is evident that reserpine (with or without chlorothiazide) is an occasionally effective regimen to maintain continued blood pressure reduction in mild hypertension when the drugs are given properly and proved to be effective If you happen to belong to the more optimistic school of thought which believes that prolonged blood pressure reduction even in mild cases of hypertension may postpone or prevent the terminal complications of the disease I suggest that you make a prolonged trial of reserpine in every mildly hypertensive subject to test the effective

TABLE 3 RECOMMENDED PROGRAM FOR TREATMENT OF MILD HYPERTENSION WITH RESERPINE

STAGE	DAILY DOSE	DURATION	OBSERVATION	EVALUATION		
				If Reduction of B P	Pulse	Procedure
Initiation	0 75 mg	6–8 wks	B P & pulse every two weeks	None	> 15%	Omit drug
				None	None	Increase dose for two weeks then omit if no effect
				15%	None or > 15%	Start maintenance Rx
Maintenance	0 125–0 250	Indefinite	B P every three months	Withdraw Rx for six to eight weeks every one to two years to confirm effectiveness restore if blood pressure rises		

* It is useful to combine chlorothiazide and reserpine but the effect of each agent should be tested separately by appropriate addition or withdrawal tests

TABLE 4 EFFECT OF HYDRALAZINE IN HYPERTENSION

MODE OF ADMINISTRATION	DOSE	USUAL EFFECT ON BLOOD PRESSURE MAGNITUDE	TIME OF ONSET
Single intravenous	25 mg	−30/−30	Immediate
Single oral	100 mg	−20/−30	30–60 min
Continuous	600 mg/day	−10/−10	Immediate or delayed tolerance?
Withdrawal			

ness of the regimen using the outline presented in Table 3 before going on to other forms of treatment

THERAPEUTIC USE OF HYDRALAZINE (APRESOLINE)

In Table 4 are presented our personal impressions of the effectiveness of hydralazine as a sole antihypertensive agent, and in Table 5 the important side effects are summarized

Acute parenteral or oral administration increases cardiac output and renal blood flow has a negligible effect on glomerular filtration rate and probably does not effect renal reabsorption since blood urea and other partially reabsorbed substances are not changed during treatment with hydralazine Single large doses of 50 to 100 mg are frequently accompanied by tachycardia nausea and headache to circumvent these side effects the dosage should be increased gradually (Table 6) To avoid the delayed appearance of the lupus erythematosus syndrome the final maintenance dose should not exceed 200 mg daily [1]

We have not observed sustained blood pressure reduction when the drug is administered for a prolonged period [16] Moyer has had a similar experience [13] On the other hand the Cleveland Clinic group has reported significant blood pressure reduction when this drug is used alone in the treatment of hypertension [1, 15] The discrepancy between their results and ours may depend on either the larger doses and greater duration of treatment in their series or the method of evaluating the blood pressure reduction Perhaps in the discussion Dr Freis can present evidence for the long term effective

TABLE 5 IMPORTANT SIDE EFFECTS OF HYDRALAZINE

TYPE	FREQUENCY	EFFECT ON TREATMENT	REFERENCE
Cardiac stimulation	Occasional	Reduce or Omit	11
Palpitation			
Angina			
Histamine like	Occasional*	Add antihistamine	12
Headache		Reduce or Omit	
Edema			
Arthralgia			
Gastrointestinal	Occasional	Omit	13 14
Nausea			
Active ulcer			
Delayed lupus syndrome	Uncommon†	Omit	15

* Pretreatment by ganglion blockade or reserpine reduces frequency Dosage should be gradually increased Toleration of side effects may appear

† Occurs only after 6 to 12 months of treatment reversible with drug withdrawal 5 to 10% incidence at 600 mg daily dose rare at 200 mg daily dose

TABLE 6 RECOMMENDED PROGRAM FOR TREATMENT OF MILD HYPERTENSION WITH HYDRALAZINE

STAGE	DAILY DOSE	DURATION	OBSERVATION	PROCEDURE TO FOLLOW AFTER EACH INTERVAL
Initiation	4 x 25 mg	1 week	Casual BP weekly	Increase dose if side effects permit and BP remains elevated
Increase	4 x 50 mg	"	" "	"
	4 x 75 mg		" "	"
	4 x 100 mg	"	" "	"
	4 x 125 mg		"	"
	4 x 150 mg			"
Maximal	4 x 150 mg	2–3 mos		Decrease dose progressively to 200 mg daily to avoid LE syndrome
Maintenance	1 x 50 mg	Indefinite	BP every 3 mos	If BP reduced to near normal regimen should be continued otherwise drug omitted

Background treatment with chlorothiazide 0 5 gm twice daily is recommended In severe hypertension ganglion blockers and Diuril should be started first with Apresoline as an adjuvant *The effect of each drug should be tested at intervals by carefully supervised withdrawal*

ness of hydralazine (Apresoline) from the present double blind testing program of the Veterans Administration Hospital

The system of evaluating treatment by daily blood pressure readings in the home requires less extensive planning although psychodynamic influences are not entirely excluded We have used this method infrequently to evaluate hydralazine but the remarkable experience recorded in Figure 2 deserves careful attention One may postulate either that the effects of hydralazine and salt depletion extended beyond the period of treatment or that blood pressure elevations in early stages of hypertensive disease occur in spontaneous cycles or that any method which produces a continuous normal blood pressure level in early hypertension may create a self sustaining normotension The possibility which we believe deserves most serious consideration is the one last mentioned Such a theory might also explain the cures reported by Perry and Schroeder[17] after prolonged hydralazine hexamethonium therapy

Impressed by their results we attempted to reproduce them by adding hydralazine to the regimen of a number of patients who were successfully controlled by ganglion blocking drugs but exhibited no signs of cure" of their disease [18] We sought to determine whether adding hydralazine would result in self sustained normotension would reduce the orthostatic blood pressure gradient and would make the regimen more tolerable The results are summarized in Table 7 It will be seen that the addition of hydralazine reduced the requirement for ganglion blocking agents in three subjects but did not alter the orthostatic gradient In one case (F W) the blood pressure rose when hydralazine was stopped In two subjects (A C and E L) there

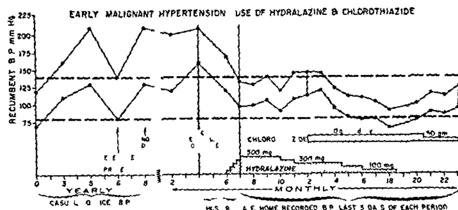


Fig 2 Effect of hydralazine-chlorothiazide treatment in severe hypertension

TABLE 7 EFFECT OF ADDITION OF HYDRALAZINE TO GANGLION BLOCKING DRUGS IN SEVERE HYPERTENSION

PT	AVERAGE STANDING BLOOD PRESSURE (mm Hg)			INCREASE IN BLOOD PRESSURE WITH RECUMBENCY (mm Hg)			MECAMYLAMINE DOSAGE (mg/day)	
	Before	During	After	Before	During	After	Before	During and After
				Hydralazine Series				
A C	119/107	155/86	148/109	66/7	11/9	32/1	65	30
W D	145/92	151/93	120/88	33/19	26/15	74/32	27 5	35
S E	143/92	129/91	123/80	57/13	21/9	86/21	55	60
F W	167/115	139/97	158/116	34/7	41/7	33/5	20	15
E L	154/114	131/81	143/93	58/126	30/97	35/12	40	20
				Placebo Series				
E H	125/75	124/73	120/69	49/4	24/4	32/8	7 5	7 5
L M	179/81	158/100	163/101	36/41	69/20	53/19	45	45

Average of two weeks of standing blood pressure readings recorded twice daily in the home at the end of a period of 5[illegible] to 58 weeks of mecamylamine therapy and after six months during which Apresoline 600 mg daily or placebo had been added Patients were asked to reduce the dose of ganglion blocking agent as necessary to maintain a normal standing blood pressure The dosage requirement of mecamylamine was reduced in three cases They were then asked to omit hydralazine and to leave the dosage of mecamylamine unchanged for a two-week period The average blood pressure of the last three days of the withdrawal period is shown in the right hand column A rebound rise was seen in one case only (F W)

was only a slight rise in blood pressure within two weeks after hydralazine withdrawal These may have been early examples of a self sustaining blood pressure reduction attributable to hydralazine but the over all results of our experiments were disappointing I hope that Dr Perry who helped us to plan these experiments will comment on the results There were admittedly many differences between his technique and ours such as the shorter treatment period the use of a different ganglion blocking agent and a different method of recording the blood pressure The most important difference may be that Drs Perry and Schroeder give larger doses of drugs and insist on such a meticulous management of the disease that the systolic sitting blood pressure rarely has a chance to exceed 140 mm Hg Such a deadly serious attack on the disease must "kill or cure" I am glad to see the cures and believe that had we been made of sterner stuff we would have had "cures" ourselves

To apply this reasoning to the case cited in Figure 2 it is possible that prompt and vigorous suppression of the hypertension regardless of the means by which it was done accomplished the "cure" and that neither hydralazine nor chlorothiazide deserves the credit We have used this combination of drugs in other cases with little success and must reluctantly conclude from our experience that hydralazine has shown little additive value in the management of hypertension

SUMMARY AND CONCLUSIONS

In about one half of the cases of mild and early hypertension reserpine with or without chlorothiazide has been proved effective The treatment should be thoroughly evaluated by observing the effects of addition and withdrawal This will avoid the unnecessary use of these drugs but will obtain optimum benefit in responsive subjects

The acute depressor effectiveness of hydralazine (Apresoline) is admitted but controversy exists concerning its long term effects on the blood pressure When hydralazine is withdrawn from a treatment regimen in which it has been combined with ganglion blocking agents or chlorothiazide (Diuril) there is little evidence of its additive value Successful results from such combination programs may depend more on maintaining continuous normotension than on the regimen employed

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Comparison of Side Effects of Different Rauwolfia Compounds

RALPH V FORD

Baylor University College of Medicine

GENERAL CONSIDERATIONS

It is important to compare the clinical results obtained with single pure alkaloids of *Rauwolfia serpentina* (e g reserpine and rescinnamine) and those obtained with preparations containing multiple active alkaloids (e g alseroxylon Roxinil or whole root) [1]

Extracts with Multiple Alkaloids (Roxinil Alseroxylon [Rauwiloid] and Rauwolfia [Whole Root]) Side actions to Roxinil alseroxylon and whole root therapy are presented in Table 1 There was very little difference among the three compounds The most frequent complaint was nasal congestion Sedation was a prominent symptom in about half of the patients Increased frequency of bowel movements (not diarrhea) was observed in the majority of the patients Weakness and fatigue were observed more frequently in the patients receiving Roxinil than in those receiving alseroxylon or the whole root but were not as severe as they were during the administration of reserpine

Single Alkaloids (Reserpine and Rescinnamine) The degree of sedation (but not the incidence) was more marked following reserpine administration than it was following the administration of the extracts containing multiple alkaloids A number of the patients who complained previously of nervousness and irritability became calmer and more tranquil (Table 1) Although the incidence of sedation in patients receiving reserpine and rescinnamine did not differ greatly the degree of somnolence was much less in the patients receiving rescinnamine The incidence and intensity of the bradycrotic response and nasal congestion were less with rescinnamine than with reserpine and the preparations containing multiple alkaloids Depression accompanied by anxiety observed in a number of patients receiving reserpine was not seen during therapy with rescinnamine

TABLE 1

Summary of Pharmacodynamic Responses (Beneficial and Untoward) to Different Extracts of Rauwolfia

	[illegible]		Alseroxylon		Rauwolfia (Whole Root)		Reserpine		Rescinnamine	
	No.*	% †	No.*	% †	No.*	% †	No.*	% †	No.*	% †
Total number treated	40	100	118	100	42	100	[illegible]	100	84	100
Side effects										
Beneficial										
Blood pressure reduction	[illegible]	65	60	51	23	[illegible]	[illegible]	[illegible]	40	48
Bradycrotic response	28	70	[illegible]	[illegible]	31	74	44	71	46	[illegible]
Sedation	[illegible]	50	63	53	[illegible]		[illegible]	47	[illegible]	[illegible]
Sense of well-being	16	40	67	57	1	[illegible]	[illegible]	35	23	[illegible]
Untoward										
Nasal congestion	[illegible]	55	[illegible]	[illegible]	31	[illegible]	40	63	42	51
Diarrhea	5	13	7		3	7	3	[illegible]	6	7
Increased appetite	24	60	[illegible]	61	26	[illegible]	[illegible]	60	[illegible]	53
Weight gain	19	48	[illegible]	[illegible]	[illegible]	[illegible]	31	[illegible]	34	40
Fatigue and weakness	16	40	13	11	1	[illegible]	[illegible]	44	13	15
Dizziness	1	[illegible]	[illegible]		[illegible]	10	13	1	[illegible]	5
Nightmare	4	10	7	6	2		[illegible]	[illegible]	3	4
Dry [illegible]	1	3	2		1	2	1	2	0	
Impotence	2	5	1	1	1	2	2	3	0	
Syncope	0		0		0		1		1	1
Muscular aches	3	8	1	1	2	5	6	10	0	

* Number of patients showing this particular response to the specified drug

† Patients presenting side-effect expressed as per cent of total number of patients treated with this particular [illegible]

COMPARISON OF PSYCHIATRIC EFFECTS OF ALSEROXYLON AND RESERPINE

It appears that the two most significantly different compounds are alseroxylon and reserpine Since there has been a consistent therapeutic protocol for all our patients we have been able to compare these preparations as to their relative toxicity We divided the subjective and objective pharmacologic effects of reserpine and alseroxylon into two main categories beneficial and adverse (Table 2)

Of the 120 patients receiving reserpine 43 per cent experienced a mild to moderate sedative effect A sense of well being was observed in 11 per cent Of the 332 patients receiving alseroxylon 81 per cent exhibited a moderate sedative effect and a sense of well being was noted by 65 per cent

We divided the adverse effects into mild moderate and severe The mild group was arbitrarily composed of (1) weakness and fatigue (2) malaise and (3) dizziness Moderate adverse effects consisted of (1) nightmares and (2) insomnia Reactions classed as severe were (1) agitation (2) depression and (3) agitated depression

TABLE 2

1 A D D O BE EFICI L A E ECTS OF RAL OLFI

	S TH N		MO S		MO E TH N T		M S		T L			
	R p		*Al yl*		*R p*		*Al yl*		*R p*		*Al yl*	
	N m b	P Ce t	N m b	P Ce t	N m ber	P Ce t	N m b	P C t	N m be	P C t	Num b	P Ce
ENEFIC												
B dy d	2		0		90	75	315	9	9?	77	31	9
Sed t	19	16	133	40	32	2	13	41	51	43	268	81
W ll be g	4	3	34	10	10	8	2 0	5	14	11	281	85
M SE												
W k d f i g	1	13	?05	62	88	73	?2	2	103	86	277	84
M l se	6	5	160	48	8	68	58	17	88	73	18	6
D zz	5	4	41	12	57	48	55	17	6	52	96	29
M ER E ADV R												
N ghtm	10	8	3	10	54	45	28	8	64	53	60	18
I som	10	8	6	2	51	43	15	5	61	51	1	7
E ER ER												
Ag t i	6	5	4	1	31	6	9	3	37	31	13	4
D p on	6	5	3	1	12	10		1	18	1	5	2
Ag t i d d p	6	5	1	0 3	12	10		0	18	15	3	0 9

O t l th th m th ft t t f th py b t ympt m t d f r m th three m th ft th py w l t d

Reserpine Of 120 patients receiving reserpine mild adverse effects were observed in one half to three fourths Moderate adverse side reactions were less frequent about 50 per cent Severe adverse side reactions were noted in a smaller group Agitation was observed in 31 per cent and persisted for more than three months in 26 per cent Depression occurred in 15 per cent and lasted more than three months in 10 per cent Serious agitated depression was observed in 15 per cent and 10 per cent of the patients experiencing this reaction did so for more than three months

TABLE 3

INCIDENCE OF MENTAL SYMPTOMS RESULTING FROM RAUWOLFIA THERAPY FOR HYPERTENSION IN PATIENTS WITH PREVIOUS NEUROPSYCHIATRIC DIAGNOSES

SYMPTOMS	RESERPINE*		ALSEROXYLON†	
	Number	*Per Cent*	*Number*	*Per Cent*
Mild	29	93 5	41	93 2
Moderate	22	71 0	13	29 5
Severe	10	32 2	4	9 1

*Total patients who had received previous neuropsychiatric diagnoses 31

†Total patients who had received previous neuropsychiatric diagnoses 44

Alseroxylon The incidence of mild adverse effects among the 332 patients receiving alseroxylon for hypertension was fairly high but only about one fifth of the group had these symptoms for more than three months Moderate adverse side reactions occurred in less than one fifth of the patients Severe adverse side reactions were much less frequent with alseroxylon than with reserpine

To determine the relation between the occurrence of adverse side reactions and neuropsychiatric disorders we reviewed the cases in which the patients had received previous neuropsychiatric diagnoses (Table 3) These patients were significantly more prone to exhibit the above reactions to both drugs than were patients who had not had neuropsychiatric diagnoses

To determine the relation of reserpine dosage to the occurrence of adverse side reactions we compared the incidence of reactions among patients receiving 1 mg or more daily and among patients receiving less than 1 mg per day We did not note a marked difference in the incidence of mild and moderate adverse reactions but there appeared to be a greater frequency of severe reactions at the higher dose (15 per cent) than at the lower dose (20 per cent) Doses of alseroxylon ranging from 4 mg to 12 mg daily did not produce significantly different reactions

CONCLUSIONS

We conclude from the data presented that alseroxylon is an antihypertensive agent of equal therapeutic efficiency to reserpine in the treatment of hypertension but that it has significantly less toxicity One must use these agents cautiously in cases in which the patients have had previous neuropsychiatric diagnoses Finally the dose of reserpine should be the smallest one that is effective for the specific case (The Food and Drug Administration suggests that this should not exceed 0 25 mg daily)

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Clinical Use of Veratrum Alkaloids

EDWARD MEILMAN

State University of New York Downstate Medical Center

Therapy in hypertensive cardiovascular disease continues to be largely empiric except for the small number of patients amenable to specific curative therapy usually surgical the others receive a variety of hypotensive drugs and measures whose efficacy is measured in terms of hypotensive action safety and freedom from side effects It has not yet been possible to separate hypertension nosologically according to the response to different therapeutic programs

At present the medical measures most widely used in treating hypertension are salt restriction diuretics ganglionic blocking drugs Rauwolfia derivatives and hydralazine These measures are not uniformly successful toxic reactions of severe nature and even death have followed several of them the mechanism of hypotension induced by the ganglionic blockers is unphysiologic and disturbances of autonomic functions may be marked For these reasons the use of Veratrum alkaloids either as biologically standardized alkaloidal mixtures or as pure alkaloids continues to have a useful though limited role

The hypotensive ester alkaloids from Veratrum exert their action in a unique fashion differing from all other hypotensive agents now in use Chemoreceptors in the heart and great vessels of the chest and in the carotid sinuses are affected by these drugs to send afferent stimuli up the vagus nerves and cause a reflex fall in blood pressure through a generalized vasodilatation and fall in heart rate The latter is vagal and can be blocked by atropine These alkaloids also have a direct central effect on the brain which causes hypotension without bradycardia They are not adrenergic blockers or sympatholytic hence no disturbance in postural or other autonomic reflexes occurs Cardiac output is not increased There is vasodilatation in all peripheral circuits including the brain and kidneys This integrated response would appear to be the most desirable physiologically in the empiric therapy of essential hypertension However for therapy with Veratrum to have a rational basis one must postulate hypertension due to a disturbance in receptor mechanisms resulting in an abnormal "setting" of central blood pressure control Emphasizing the empiric nature of present hypotensive therapy Veratrum esters like the more commonly used hypotensive drugs exert their effect regardless of the etiology of the hypertension

The usefulness of Veratrum is limited by the narrow margin between therapeutic and toxic doses approximating 30 per cent In some individuals toxic and therapeutic doses coincide in others toxic effects may appear without any blood pressure effect These toxic effects are dramatic and distressing but I know of no fatalities from them Overdosage is first heralded by substernal burning and discomfort which may spread to the throat hands abdomen and perineum Nausea hiccups and vomiting frequently

follow Severe bradycardia and varying degrees of heart block may result These effects are all transient Severe hypotension can be readily reversed by subcutaneous administration of 25 to 35 mg of ephedrine The bradycardia which accompanies the fall in blood pressure and disturbances in conduction can be overcome by 0 5 mg of atropine without as a rule eliminating the hypotensive response Atropine in some cases may abolish the hypotensive response along with the bradycardia

Parenteral and particularly intravenous administration of Veratrum alkaloids has the following merits A predictable fall in blood pressure from a dose based on the patient s weight can be obtained in a reasonable length of time there is no increase in cardiac output or disturbance of homeostatic autonomic functions the drug does not interfere with use of subsequent measures or drugs it has no serious complications of its own In almost all cases especially in patients with acute hypertensive episodes intravenous administration will lower the pressure

PARENTERAL ADMINISTRATION OF VERATRUM ESTERS (PROTOVERATRINE [VERALBA] ALKAVERVIR [VERILOID])

The intravenous dose of *protoveratrine* (Veralba) is 1 5 to 1 9 mcg /kg given over two minutes Twenty mcg are added at 10 minute intervals until a satisfactory level of blood pressure is reached In over two thirds of all cases this program will lower the blood pressure to 150/100 or less A continuous infusion rate of about 1 mcg /min will maintain the hypotensive effect

The subcutaneous or intramuscular dose of protoveratrine is 4 to 6 mcg /kg The initial dose should be 4 mcg /kg (or 0 3 mg for a 75 kg person) If there is no response in one half hour an additional 0 15 mg is given If there is a partial response only 0 10 mg is necessary The effective dose can then be repeated at intervals of 6 to 8 hours without cumulation An occasional patient will show an effect for 12 hours after the injection When other Veratrum preparations are used close attention must be paid to accompanying detailed directions concerning administration

The best indication for the use of parenteral protoveratrine or other alkaloidal mixtures from Veratrum is in hypertensive encephalopathy such as occurs in acute glomerulonephritis toxemia of pregnancy hypertension complicating steroid treatment or the malignant phase of hypertension The encephalopathy of acute glomerulonephritis or toxemia responds in an almost specific manner Oliguria is not a contraindication of the use of Veratrum

The following case indicates the response to protoveratrine of hypertension complicating steroid treatment in lupus erythematosus

Case I (R A) A 30-year-old female was admitted to the hospital seven months after the diagnosis of lupus erythematosus was established She had been treated with prednisone in doses of 10 to 40 mg daily Attempts to decrease the dose of steroid aggravated the disease when steroid dosage was increased her blood pressure began to rise Three days before admission albuminuria appeared and she became drowsy On admission she was semicomatose Her face was moon shaped Her blood pressure was 200/150 The skin of the lower extremities was blotchy and covered with numerous petechiae The hands and feet were cold and cyanotic The optic fundi showed bilateral papilledema hemorrhage and exudates with a marked degree of arteriolar spasm The heart was enlarged to the left and a gallop rhythm was present Since the BUN was normal a diagnosis of hypertensive encephalopathy probably secondary to steroid administration appeared likely

It was considered inadvisable to omit prednisone suddenly for fear of exacerbating the lupus and therefore treatment with protoveratrine (Veralba) in doses of 0.3 mg parenterally every 3 to 4 hours was begun. Under this program control of the diastolic blood pressure at levels of approximately 100 mm Hg was obtained. With control of blood pressure it was considered safe to give 200 mg of hydrocortisone intravenously. Repeated injections of protoveratrine in dosage of 0.75 mg every 8 hours gave continuous intermittent control of the blood pressure so that at the time of discharge the average was 140/90.

The gallop rhythm disappeared when the blood pressure was reduced. There was some clearing of sensorium on the third day and at the end of the week the patient was quite rational. The steroid dosage was rapidly reduced from 200 mg to 40 mg daily without any aggravation of her clinical state thus supporting the impression that the response was due to hypotensive medication rather than steroid administration. The papilledema hemorrhages and exudates cleared in three weeks. The patient survived for two and a half years and finally succumbed to her disease.

The above case illustrates a severe instance of hypertensive encephalopathy in which administration of protoveratrine made it possible to continue and even increase steroid dosage without aggravation of the hypertensive state.

Malignant hypertension especially with threatening or actual loss of vision is another indication for prompt control of severe hypertension by parenterally administered Veratrum alkaloids.

Case II (G.B.) This 51 year-old carpenter was admitted in July 1957 with a history of increasing exertional dyspnea anterior chest pain and diminution in vision. During the preceding year he had lost 44 pounds and become impotent. Hypertension had been known for several years but he had not received treatment until five months before entry at which time he was given bed rest low-salt diet and pentolinium. This program apparently was ineffective and when visual deficit appeared he entered the hospital. He was a thin man who appeared chronically ill. There was gross impairment of vision so that he could not recognize faces 15 feet away. His blood pressure averaged 200 to 220/130 to 140. The optic fundi showed extreme papilledema with irregular markedly spastic arterioles A-V nicking silver wire effect hemorrhage and exudates. The heart was markedly enlarged to the left. There was no gallop. His BUN ranged from 37 to 40 mg per cent. The urine had 2+ protein and 1.010 specific gravity. The electrocardiogram showed right bundle branch block, evidence of left ventricular enlargement and myocardial disease. The intravenous pyelogram showed fair function.

He was treated initially with an intravenous infusion of protoveratrine receiving 0.22 mg over 70 minutes which reduced his blood pressure from 210/130 to 150/100 without side effects. Thereafter he received 0.4 mg of protoveratrine subcutaneously at 6-hour intervals. He proved unusually responsive to protoveratrine the blood pressure usually falling to levels of 124 to 138/70 to 90 without toxic effects. At the end of 12 days when no protoveratrine was available the blood pressure which had not gone above 180/100 while the patient was on therapy rose to [illegible]0 to 235/130 to 135. When the drug was resumed he responded as previously. At the end of three weeks of therapy the papilledema hemorrhage and exudates in the optic fundi had cleared. He had lost 8 pounds. His BUN was now 27. Urinary protein had diminished to a trace and the patient was quite elated that he had been able to have an erection again. His vision had improved steadily so that he could now read all but fine print in a newspaper.

The acute situation having been controlled the patient was transferred to oral medication with mecamylamine reserpine and a 500 mg sodium diet. On this therapy his remission has been maintained for one and a half years. At present his urine has a trace of protein. The optic fundi are grade II. The BUN has varied between 31 and 47 the most recent value being 36. He is employed as a key maker.

The above case illustrates the prompt control of severe hypertension that can be obtained with restoration of visual loss paralleling blood pressure control.

Veratrum can generally not be used parenterally for prolonged periods

of many weeks because of the inconvenience of repeated injection usually necessitating hospitalization and because of the development of nausea or vomiting Ideally these drugs should be used to control an acute situation Later oral medication with other hypotensive drugs or occasionally with Veratrum alkaloids can be substituted for long term therapy

ORAL ADMINISTRATION

Protoveratrine consists of two alkaloids A and B the B having an extra hydroxy group Parenterally A and B have similar hypotensive activity and dosage does not depend on their relative amounts By mouth they differ markedly A is the major active hypotensive principle and has a narrow therapeutic range in mixtures of the two B is much less potent It is therefore necessary that either A and B mixtures of constant composition (such as Veralba) or pure protoveratrine A alone be used for oral administration Other oral preparations are Veriloid Vertavis and Unitensin

The predictability of response to parenteral Veratrum compounds is not evident with oral administration In general the oral dose is 7 to 10 times the intravenous dose suggesting either poor intestinal absorption or degradation in the gastrointestinal tract Thus far no Veratrum alkaloids have been found whose oral and parenteral doses are the same or which have hypotensive but not emetic properties Most reports concerning oral use of Veratrum alkaloids state that hypotensive response free of toxic effects can be expected in only 20 to 30 per cent of patients Even in this small group the desirable hypotensive responses may not persist beyond several weeks to months However even among authors frankly skeptical of the benefits of oral Veratrum alkaloids one usually finds at least one case in which there was a marked response often to normotension These cases may represent not more than 5 per cent of the total The following case report of a patient with malignant hypertension is an example

Case III (H K) This 41 year-old female executive came to the United States in June 1952 to have a sympathectomy for malignant hypertension the diagnosis having been based on the presence of papilledema hemorrhages and exudate Her previous therapy had consisted of salt restriction and phenobarbital Her hypertension was of unknown duration and had been asymptomatic until visual changes were noted Examination revealed obesity and eye changes Blood pressure ranged from 180 to 200/110 to 135 There was left axis deviation on the electrocardiogram but no significant cardiac enlargement The urine was normal

She was treated with protoveratrine by injection but because of the marked response was soon changed to oral medication On oral therapy her blood pressure varied from 150 to 160/100 to 110 She received a 1 gm sodium diet The eye findings cleared rapidly except for the exudate which persisted for several months She returned to Israel on oral protoveratrine which she continued until 1958 Toxic reactions (vomiting) occurred only three times during this period For about one year she received Rauwiloid but complained that it interfered with her effectiveness and therefore took it irregularly She made some effort to restrict salt in her diet She has been examined yearly The blood pressures recorded in 1957 ranged from 128/80 to 160/110 (a casual reading) and in 1958 casual readings were 142 to 154/95 to 108 Her eyes now show grade II fundi There is no trace of old exudate Electrocardiogram and heart size are unchanged over six years albumin has never appeared in the urine At present she eats virtually a normal diet and has even begun to omit protoveratrine She is actively engaged in executive activities

This case is an example of good response to oral protoveratrine Not only were the accelerated features of her hypertension reversed but she was

spared the operation of sympathectomy and did not have to endure the inconveniences of ganglionic blocking drugs

Oral Veratrum alkaloids should be tried in (1) patients who demonstrate almost normotensive levels with parenteral Veratrum without vomiting and (2) patients with severe or unacceptable side effects from the other commonly used hypotensive drugs The details of oral administration vary with the preparation used As with other hypotensive agents synergistic or at least additive effects are obtained by combination with diuretics and Rauwolfia

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Iproniazid and other Amine Oxidase Inhibitors in Arterial Hypertension with or without Complicating Angina Pectoris

WILLIAM HOLLANDER and ROBERT W WILKINS

Boston University School of Medicine

INTRODUCTION

Serotonin a naturally occurring compound may play an important role in the pathogenesis of arterial hypertension Some findings in hypertensive man suggest such a possibility (1) Serotonin is a vasoactive substance which is capable of decreasing or increasing the blood pressure and (2) drugs such as Rauwolfia BAS (benzyl analogue of serotonin) and iproniazid

which effectively lower the blood pressure also alter the metabolism of serotonin However the manner in which serotonin might affect the blood pressure is not clear especially since some of these antihypertensive agents appear to have opposite effects on serotonin metabolism[1,2]

A number of workers have reported that iproniazid a compound that prevents the inactivation of serotonin by inhibiting monoamine oxidase[3] is effective both as an antihypertensive and anti anginal agent[4-9] The present study which includes our clinical experience of one year with iproniazid* in over 50 hypertensive subjects has confirmed these observations Primarily the study was undertaken in an attempt to clarify the mode of action of iproniazid and other amine oxidase inhibitors on the blood pressure and particularly the blood pressure responses to serotonin

PROCEDURES AND RESULTS

The characteristic types of blood pressure responses to an intravenous injection of serotonin are shown in Figure 1 Serotonin may decrease the

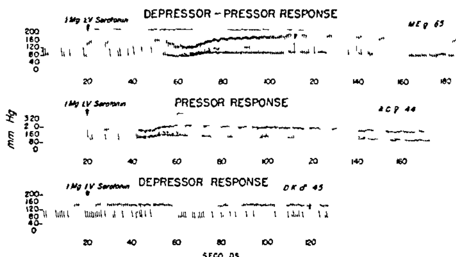


Fig 1 Chart showing the typical arterial pressure responses to intravenous serotonin

blood pressure (depressor effect) increase the blood pressure (pressor effect) or produce a combination of these effects (depressor pressor effect) The duration of action of serotonin on the blood pressure is brief and is accompanied by an increase in the pulse rate which in most cases lasts from *20 to 90 seconds*

The effects of antihypertensive agents which are said to affect serotonin metabolism were studied in the laboratory to determine whether they might alter such blood pressure responses to serotonin The first of these compounds was the benzyl analogue of serotonin (Wooley s BAS†) which had been shown to have a clinical action resembling that of Rauwolfia in being mildly antihypertensive and moderately sedative[10] Typical effects of intravenous BAS on the blood pressure responses to serotonin are shown in

* Kindly supplied by Hoffmann LaRoche Inc
† Chemically known as 1 benzyl 2 methyl 5 methoxy tryptamine HCl

Figure 2 The upper tracing shows that intravenous serotonin during the control period produced an initial decrease in the blood pressure which was then followed by an increase After intravenous BAS there was a prolongation of the depressor effect of serotonin but a disappearance of the pressor effect In a tracing from another patient similar but less striking results were obtained These observations suggest that the effect of intravenous BAS is to promote the depressor action if not to lessen the pressor action of serotonin on the blood pressure

As compared with intravenous BAS oral BAS or reserpine given orally or parenterally had no effect on the blood pressure responses to intravenous serotonin[11]

The effects of two monoamine oxidase inhibitors iproniazid and JB516

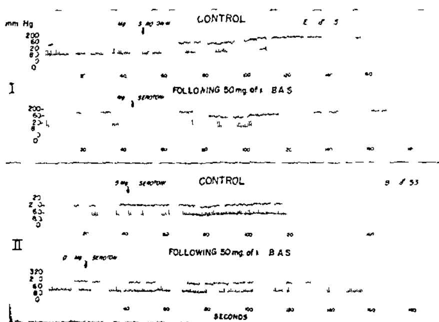


Fig 2 Chart showing the effects of intravenous BAS (benzyl analogue of serotonin) on the arterial pressure responses to intravenous serotonin

(1 phenyl 2 hydrazinopropane) * on the blood pressure responses to serotonin are shown in Figure 3 In the upper (control) tracing of experiment I intravenous serotonin produced a slight and brief reduction in blood pressure After two weeks of oral iproniazid in a daily dosage of 150 mg the same intravenous dose of serotonin produced a greater reduction in blood pressure and for a longer period of time than the same dose of serotonin did in the control study In the middle tracings (experiment II) similar but more striking results were obtained with JB516 In the lower tracings (experiment III) serotonin produced an increase in the blood pressure in the control study However after the oral administration of JB516 serotonin caused no rise but rather a slight decrease in the blood pressure

* Kindly supplied by Lakeside Laboratories

Although serotonin may have a variable effect on the blood pressure when repeated weeks apart in the same subject the preliminary results of 16 tests in five subjects suggest that amine oxidase inhibitors promote the depressor action of serotonin on the blood pressure in a manner resembling the effects of intravenous BAS However a greater number of observations are necessary including some after intravenous drug administration before the mode of action of these amine oxidase inhibitors on the blood responses to serotonin can be established

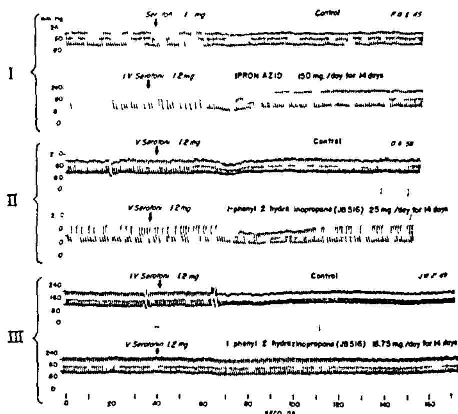


Fig 3 *Chart showing the arterial pressure responses to intravenous serotonin before* and after the oral administration of the monoamine oxidase inhibitors iproniazid and JB516 in three hypertensive subjects

Monoamide oxidase inhibitors such as iproniazid JB516 Ro 5 0831/1 (1 benzyl 2 (5 methyl 3 isoxazolylcarbonyl)hydrazine)* may have some other properties resembling those of BAS Thus in two of the five subjects the symptomatic side effects of serotonin including hyperventilation and dyspnea did not occur following treatment with these agents In none of the subjects were the side effects of serotonin increased by the amine oxidase inhibitors

The clinical actions of iproniazid and other amine oxidase inhibitors were also examined The effects of iproniazid in a splanchnicectomized hyperten

* Kindly supplied by Hoffmann LaRoche Inc

sive subject with angina pectoris are illustrated in Figure 4 In this subject Rauwolfia had had no appreciable effect on the blood pressure It likewise did not alter the episodes of angina pectoris which occurred about 16 times a week Following the institution of iproniazid in a daily dosage of only 50 mg the patient became more anxious and irritable but nevertheless had striking reductions in blood pressure and in the number of attacks of angina pectoris but without a change in the electrocardiographic pattern of left ventricular hypertrophy During continued iproniazid therapy there also was a slight decrease in serum cholesterol without a significant change in serum transaminase values These findings do not establish that the reductions in

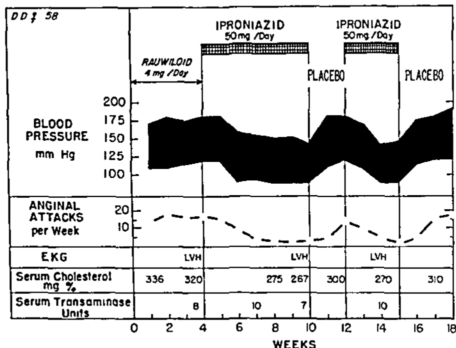


Fig 4 Chart showing the effects of iproniazid on blood pressure anginal attacks EKG and serum cholesterol and transaminase levels in a splanchnicectomized hypertensive subject with angina pectoris

number of anginal attacks and in serum cholesterol were due to a direct action of iproniazid since such changes may also occur following a reduction in blood pressure by other antihypertensive agents However they do indicate that the relief of angina pectoris following iproniazid may occur without an obvious improvement in the psychologic state of the patient

The effects of the different amine oxidase inhibitors in a hypertensive subject with angina pectoris are shown in Figure 5 Iproniazid JB516 or Ro5-0831/1 in combination with chlorisondamine (Ecolid) had no greater effect on the blood pressure than chlorothiazide added to chlorisondamine However the amine oxidase inhibitors as compared with chlorothiazide produced a marked reduction in the number of anginal attacks For example before the institution of iproniazid the patient experienced about 38 anginal

attacks per week but after iproniazid in a daily dosage of only 50 mg he averaged about three attacks of angina per week and was able to increase his activities and return to work Although the angina pectoris was markedly improved by treatment the electrocardiographic tracings following standard exercise continued to show changes consistent with coronary insufficiency The serum cholesterol and transaminase levels also did not change significantly with treatment These and other studies indicate that the improvement of angina pectoris apparently caused by the monoamine oxidase inhibitors in hypertensive subjects may occur without a reduction in blood

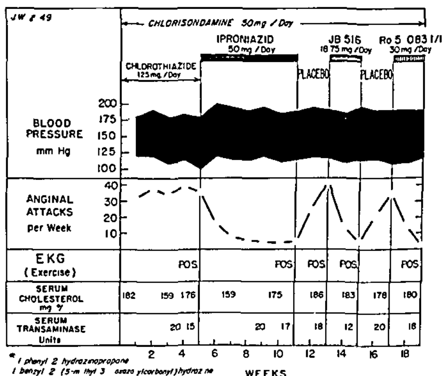


Fig 5 Chart showing the effects of the monoamine oxidase inhibitors iproniazid, JB516 and Ro5 0831/1 on blood pressure anginal attacks EKG and serum cholesterol and transaminase levels in a hypertensive subject with angina pectoris

pressure They also suggest that changes in serum cholesterol during treatment may be related to the changes in blood pressure

The blood pressure responses to iproniazid and JB516 in a resistant case of hypertension without angina pectoris are shown in Figure 6 Even though the subject was receiving pentolinium hydralazine and reserpine the blood pressure remained at hypertensive levels After the pentolinium was replaced by iproniazid in a daily dosage of 150 mg per day the blood pressure in the sitting position gradually decreased toward normal During this period the patient developed postural hypotension as well as dryness of the mouth constipation and urinary difficulty—side effects resembling those produced by ganglionic blocking agents After the dosage of iproniazid was decreased to 50 mg per day these side effects as well as the hypotensive action of

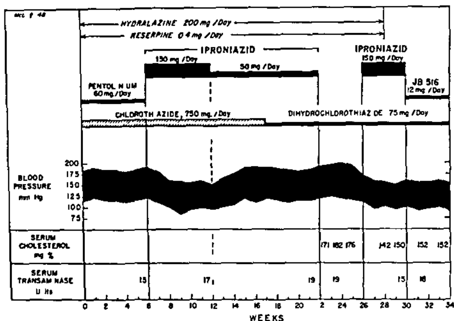


Fig 6 Chart showing the effects of iproniazid and JB516 (1 phenyl 2 hydrazinopropane) on the blood pressure and serum cholesterol and transaminase levels in a subject with essential hypertension

iproniazid disappeared When JB516 was substituted for iproniazid in the last part of the study the reduction in blood pressure was maintained without side effects except for orthostatic hypotension These actions of JB516 have been previously described by Gillespie Terry and Sjoerdsma [1] The serum transaminase levels remained normal during treatment whereas serum cholesterol decreased slightly in association with lowering of the blood pressure

Most of the subjects while on iproniazid developed a feeling of well being and reassurance as well as an increase in psychomotor activity However iproniazid in a daily dosage of 25 to 150 mg caused a number of side effects which are listed in Table I In general the frequency and severity of the side reactions varied directly with the dosage of the drug In an average daily dose of 50 mg iproniazid was usually well tolerated whereas in higher dosage effects were frequent and occasionally severe

TABLE I SIDE EFFECTS OF IPRONIAZID IN 51 CASES

Blurring of Vision	3	Paresthesia	5
Dryness of Mouth	15	Reduced Libido	6
Constipation	14	Anxiety	4
Urinary Difficulty	3	Irritability	4
Orthostatic Dizziness	5	Insomnia	9
Orthostatic Syncope	1	Epigastric Distress	6
Orthostatic Angina	1	Jaundice	0
Headache	3	Weight Gain	9
Neuralgia	2	Ankle Swelling	3
		Elevated Serum Transaminase	0

The occurrence of blurring of the vision dryness of the mouth constipation urinary difficulty and orthostatic hypotension suggests that iproniazid has a ganglionic blocking action It is interesting that angina pectoris was precipitated in one case during a marked fall in blood pressure in the upright position Although iproniazid is capable of producing severe liver disease in rare instances no impairment of liver function as indicated by the appearance of jaundice or an elevated serum transaminase was detected in this small series of cases

The blood pressure effects of iproniazid in 51 hypertensive subjects are summarized in Table 2 The blood pressure responses were studied at two dose levels because of the striking difference in side effects that occurred at these dosages Iproniazid itself was capable of reducing the blood pressure However the compound was considerably more useful and effective when combined with other drugs The latter agents included Rauwolfia hydralazine chlorothiazide dihydrochlorothiazide and ganglionic blockers

TABLE 2

IPRONIAZID IN 51 SUBJECTS WITH ARTERIAL HYPERTENSION

	Iproniazid Dosage (mg/day)	No of Cases	No of Responders (B.P↓ > 14/9)	Average B P Reduction (mm Hg)	Range of B.P Reduction (mm Hg)
IPRONIAZID ALONE	25 75 (50)	7	1	7/4	10/5 - 40/20
	100 150 (125)	5	2	19/9	30/15 60/25
OTHER DRUGS + IPRONIAZID	25 75 (50)	39	18	17/9	20/10 - 55/25
	100 150 (125)	11	7	24/13	20/10 60/30
GANGLION BLOCKERS or SYMPATHECTOMY + IPRONIAZID	25 50	5	3	22/12	20/15 55/25

In a small dosage of 25 to 75 mg per day iproniazid when added to other drugs produced a further lowering of the blood pressure in about half the subjects tested The range of blood pressure reduction varied from 20/10 to 55/25 mm Hg Although iproniazid in the higher dose range had a more potent antihypertensive action it produced more side effects than it did in smaller dosage For example of 11 subjects who did not respond with a blood pressure reduction to an average daily dose of 50 mg of iproniazid four responded to an average daily dose of 125 mg of iproniazid but had increased side reactions

The hypotensive action of iproniazid which frequently included an additional postural hypotensive effect usually began within four to eight days

and was maximal within two to three weeks after treatment After the compound was withdrawn the hypotensive effect usually persisted for about one week but lasted in some cases as long as two to three weeks

Fourteen subjects in the hypertensive group had complicating angina pectoris which had not been relieved by Rauwolfia or pentaerythritol tetranitrate However iproniazid alone and in combination with these and other drugs produced a considerable reduction in anginal attacks in nine of 14 subjects who received dosages of the compound as small as 25 to 75 mg per day The anti anginal effects of iproniazid which are summarized in Table 3 were inconsistently related to the concomitant changes in blood pressure One subject receiving 75 mg of iproniazid daily had a complete cessation of angina and four other subjects receiving 25 to 50 mg of iproniazid had almost complete disappearance of angina Of four subjects who did not respond to an average daily dose of 50 mg of iproniazid two responded to an average daily dose of 125 mg of iproniazid The relief of angina pectoris occurred in three to 12 days after the start of the drug and persisted after the withdrawal of the drug for three to 28 days

TABLE 3

IPRONIAZID IN 14 HYPERTENSIVE SUBJECTS WITH ANGINA PECTORIS

Iproniazid Dosage (mg /day)	No of Cases	No With Reduction of Angina by >24%	Average Reduction of Angina	Range of Reduction of Angina	E K G
25 -75 (50)	14	9	42 %	25-100%	Unchanged
100 150 (125)	4	2	41 %	65-100%	Unchanged

Even though iproniazid produced a remarkable improvement in angina it did not alter the resting electrocardiogram It likewise had no appreciable effect on the electrocardiogram following exercise in six subjects all of whom continued to show electrocardiographic signs of myocardial anoxia during iproniazid treatment These findings suggest that the anti anginal effect of iproniazid might be due to an interference of pain sensation in areas of reference from the heart and not necessarily to coronary vasodilatation or to a reversal of myocardial anoxia Such a removal of the pain signal of coronary insufficiency conceivably might aggravate the basic disease process However none of the subjects who had a reduction in anginal attacks had a myocardial infarction or died during iproniazid treatment even though most of them increased their activities led a more normal life and returned to work In view of these observations additional longer term studies are necessary to establish fully the mode of action of iproniazid in angina pectoris

SUMMARY

Iproniazid especially in combination with other hypotensive drugs is an effective antihypertensive agent which frequently produces a feeling of well being In small as opposed to high dosage the compound is usually well tolerated Iproniazid in low dosage is also effective in preventing angina pectoris without necessarily producing an alteration in the blood pressure or in the electrocardiogram at rest and following exercise Hepatic damage as a complication of iproniazid treatment was not detected in the dosage used in this small series of cases One of the newer monoamine oxidase inhibitors (JB516) appears to have a higher therapeutic index than iproniazid

The clinical actions of iproniazid suggest that the compound might be classified as a slow acting ganglionic blocker as well as a monoamine oxidase inhibitor Whether these two actions of iproniazid are separate or inter related is not clear Preliminary results suggest that amine oxidase inhibitors resemble intravenous BAS (benzyl analogue of serotonin) in promoting the depressor action of serotonin on the blood pressure The main clinical use of iproniazid appears to be in the treatment of resistant cases of hypertension especially with complicating angina pectoris The agent is also worthy of trial in hypertensive patients who respond to antihypertensive drugs but who remain incapacitated by angina pectoris

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Effect of Iproniazid on Digital Vascular Norepinephrine Sensitivity*

STANLEY GITLOW MILTON MENDLOWITZ and NOSRAT NAFTCHI

Mt Sinai Hospital New York N Y

The importance of determining the process by which rapid pressor inactivation of norepinephrine (NE) occurs *in vivo* has been emphasized by the finding that primary hypertension is associated with an abnormally increased sensitivity to the pressor effects of infused NE [1] Such hypersensitivity may be caused by some defect in the metabolic pathway for NE inactivation Recent studies [3 4 5] have emphasized at least two basic mechanisms

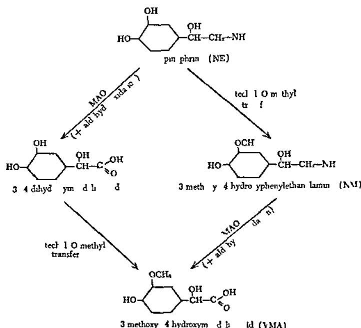


Fig 1

for *in vivo* degradation of NE one by means of oxymethylation of the hydroxyl group at carbon 3 leading to a 3 methoxy 4 hydroxy derivative of NE (NM) and the other amine oxidation of the side chain leading to a mandelic acid derivative (Fig 1) Significant quantities of 3 methoxy 4 hydroxymandelic acid (VMA) a product of these two reactions can be found in human urine [3] However it is not known which of the two metabolic

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processes is responsible for the initial rapid inactivation of NE or which occurs first in vivo Although previous animal experimentation has produced evidence both in favor of the physiologic importance of amine oxidation of NE[6 7 8 9] and opposed to it[10 11 1] no previous study of this subject has utilized the tissue of greatest clinical interest the human vasculature as the test tissue The significance of each of these metabolic pathways can be evaluated by determining NE sensitivity in the normal human subject following interference with one of these two pathways 1 Isonicotinyl 2 isopropylhydrazide or iproniazid (IIH) has been demonstrated to be a potent inhibitor of monoamine oxidase (MAO)[13 14 15] the enzyme apparently responsible for amine oxidation of the side chain of NE[3 16 17 18] There is ample evidence that IIH does not inhibit the enzyme responsible for oxymethylation of NE[4 5]

To test the hypothesis that NE hypersensitivity is related to a defect in inactivation of NE by amine oxidation in man NE sensitivity of normotensive subjects whose MAO had been inhibited by prior administration of IIH was determined

METHODS

Methods for measuring NE sensitivity in digital circulation have been presented in detail elsewhere[1 13] The primary effect of NE is to produce vascular smooth muscle contraction The work of such muscular action is a function of pressure within the blood vessels and change in their caliber following NE infusion Observations of digital blood flow and pressure following blockade of sympathetic nerve discharge by indirect heat supplemented by intravenous injection of a ganglion blocking drug permit calculation of a single radius equivalent for dilated digital blood vessels Under identical conditions similar measurements are made during NE infusion Changes in radius equivalent and mean arterial pressure resulting from this infusion are used to calculate work of vasoconstriction per mg of NE infused per minute This value reflects NE sensitivity and as such remains fairly constant in each individual Oral IIH in dosage of 4 mg /kg of body weight per day was administered to four subjects after control NE sensitivity values were determined these patients were restudied on the seventh day of IIH administration In addition four normotensive subjects whose control NE sensitivity values had been previously determined received 25 to 40 mg /kg of IIH intravenously three to four hours after which the studies were repeated Two additional normotensive subjects had a single examination each These were performed 60 minutes after 15 and 18 mg /kg of IIH respectively had been administered intravenously A preliminary study failed to demonstrate any change in digital blood pressure or flow produced by intravenous administration of IIH alone

The ability of IIH to reach and inhibit intracellular MAO in the living animal had been recently questioned[1] To determine whether IIH administered as in this study could indeed inhibit MAO *in vivo* six rabbits were sacrificed and their renal collecting tubules stained for MAO activity by the method of Koelle and Valk Jr Three of the animals received 25 to 40 mg /kg of IIH intravenously three to four hours antemortem

RESULTS

NE vascular sensitivity is expressed throughout as work of digital vaso

TABLE 1 NE SENSITIVITY DURING ADMINISTRATION OF IIH ORALLY TO 4 NORMAL SUBJECTS

WORK OF VASOCONSTRICTION (IN ERGS × 10³)/MG OF NE INFUSED/MIN	
A	B
78	45
44	31
33	44
48	54

A Control
B On seventh day of oral IIH administration

constriction in ergs per mg of NE infused per minute Results of these studies performed in four normal subjects before and after administration of oral IIH for a seven day period are presented in Table 1 It is clear that 4 mg/kg/day of IIH administered orally failed to affect NE sensitivity significantly or consistently Data presented in Table 2 on six normal human subjects similarly fail to reveal any consistent change in NE sensitivity produced by 15 to 40 mg/kg of IIH administered as a single intravenous injection 60 to 230 minutes prior to final (second) testing A third study performed on one patient 29 hours after receiving 30 mg/kg of IIH intravenously also failed to reveal a change in NE sensitivity

Results of the histochemical studies (Figs 2 and 3) consistently demonstrated the ability of IIH (in the same dosage used in the human subjects) to inhibit MAO activity in vivo

DISCUSSION

Although it is possible that IIH acts only on MAO in renal collecting tubules and not in blood vessels or is effective in rabbits but not in human subjects these possibilities seem quite unlikely in view of the recent demonstration of inhibition of amine oxidation of isotopically tagged NE [3] serotonin [4] and epinephrine by IIH administered to the living animal The dosage of IIH used in this study is quite comparable to that used in other

TABLE 2 NE SENSITIVITY BEFORE AND AFTER IIH ADMINISTERED INTRAVENOUSLY TO 7 NORMAL SUBJECTS

WORK OF VASOCONSTRICTION (ERGS × 10³)/MG OF NE INFUSED/MIN		INTRAV IIH (MG/KG)	TIME LAPSE (MIN) BETWEEN ADMIN OF IIH AND REPEAT TESTING
A	B		
	3[illegible]	15	50
	34	18	80
39	46	25	60
4[illegible]	[illegible]9	40	180
50	58	35	225
[illegible]9	3[illegible]	30	230
[illegible]	38	30	1740 (29 hr)

A Control
B After intravenous IIH
The work of digital vasoconstriction for normal subjects is 31 (mean) ± SD of 10 5

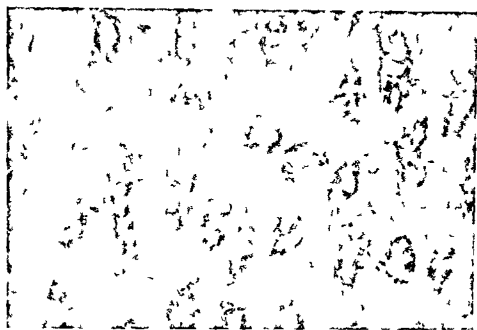


Fig 2 Photomicrograph of monoamine oxidase distribution in collecting tubules of rabbit kidney (× 410)

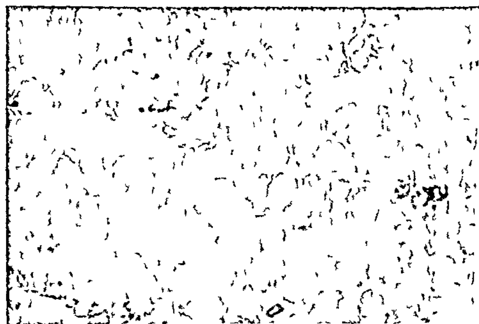


Fig 3 Photomicrograph of rabbit kidney stained for monoamine oxidase activity following intravenous administration of IIH 30 mg/kg 3 hours premortem (× 410)

studies demonstrating MAO inhibition [6, 7, 10, 14, 4, 5] It seems more probable that MAO is simply not significantly involved in the rapid inactivation of the pressor effect of NE

Von Euler found NE to be that substance released from adrenergic nerve endings which is responsible for neurogenic vasoconstriction [19] Increased neurogenic vasoconstriction as well as increased NE sensitivity have been demonstrated in primary hypertension [1, 19] Although such hypersensitivity may be attributable to muscular hypertrophy of the arteriolar walls the fact that 11 oxy 17 hydroxycorticoids can produce similar hypersensitivity in normotensive subjects in as little as 7 to 21 days without causing hypertension would appear to favor some other mechanism [20] Moreover such muscular hypertrophy might be expected in hypertension produced by pheochromocytoma and yet diminished NE sensitivity seems to be the rule in this disease [8, 9] On the other hand increased sensitivity to NE is known to follow sympathetic nerve section[17, 30] and could conceivably be caused by diminished sympathetic nerve discharge However studies of urinary catechol amines not only fail to reveal evidence for diminished adrenergic nerve activity in patients with primary hypertension but if anything the formation of NE may be somewhat above normal [18]

Since 1937 monoamine oxidase has been believed responsible for inactivation of NE[16] and in fact Burn and others have formulated a complex scheme explaining the pharmacologic activity of many sympathomimetic drugs by their effect upon this enzyme [17, 0] Although amine oxidation of NE occurs *in vivo*[3] and may even be of particular importance in the cerebral metabolism of NE it does *not* appear to be the mechanism whereby initial immediate inactivation of the direct peripheral vascular effect of NE occurs

Although the exact mechanism whereby NE elicits arteriolar smooth muscle contraction and is subsequently inactivated is unknown it appears evident that a defect in that step which limits the rate of change of NE to its pressor inactive metabolite may well be responsible for the NE hypersensitivity in primary hypertension It is tempting to suggest that this defect exists in the enzymatic change of NE to NM its pressor inactive metabolite [31] A genetically determined insufficiency of catechol O methyl transferase might then explain the etiology of primary hypertension as well as its hereditary distribution Despite the attractiveness of this theory it must be realized that cell membrane or protein binding conjugation or some other as yet ill defined mechanism may be responsible for the rapid pressor inactivation of NE It is believed that identification of this mechanism may clarify the cause of primary hypertension [3]

SUMMARY AND CONCLUSIONS

Iproniazid given by mouth or intravenously to normotensive human subjects did not alter sensitivity of their digital blood vessels to norepinephrine

Iproniazid in dosage similar to that used in the human subjects does inhibit monoamine oxidase *in vivo* in rabbits

Increased sensitivity of human digital blood vessels to norepinephrine in primary hypertension is therefore not attributable to a change or deficit in vascular monoamine oxidase It is suggested that a defect in NE metabolism caused perhaps by a deficiency in catechol O methyl transferase is responsible for this hypersensitivity

ACKNOWLEDGMENT

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Discussion

Garfield Duncan *Moderator*

Benedict Abreu	Sibley Hoobler
Albert Brust	Walter Kirkendall
Richard Dunsmore	Edward Meilman
Ralph Ford	John Moyer
Edward Freis	William Paton
Stanley Gitlow	H Mitchell Perry
Arthur Grollman	Albert Plummer
Carroll Handley	Bertram Winer
William Hollander	

Dr Duncan I judge that at times reserpine is a very effective agent At other times it does not seem to be effective At still other times a single dose may last for a couple of days Dr Hoobler what is your opinion about this?

Dr Hoobler When given parenterally reserpine is strikingly effective in about 90 per cent of subjects The effectiveness of a single parenteral dose is high in the patient with an acute hypertensive emergency The patient isn't always relieved of hypertension but he certainly is relieved of that increment of blood pressure which may make the difference between death and recovery from the hypertensive emergency

Dr Moyer Figure 1 is the blood pressure response to 4 mg of reserpine given parenterally in a patient with malignant hypertension The blood pressure decreased to normotensive levels and remained there throughout the period of drug administration Our observations confirm Dr Hoobler's statement

Dr Meilman What percentage of oral reserpine is absorbed?

Dr Hoobler I don't know There is a paradox in the use of this drug in that we usually give less parenterally than we give by mouth but here we're doing just the reverse

Dr Plummer I know that there are species differences in the way reserpine is treated in the gastrointestinal tract Published reports comparing hydrolysis of the ester in the intestine in the rat and in the dog indicate that the rat hydralizes the compound quite readily and the dog less so We also know of course that the rat is quite resistant and tolerates a very large dose orally The dog is extremely sensitive The human is comparable in sensitivity to the dog as far as dosage is concerned If there are any studies on the handling of reserpine in the intestine in the human I am not aware of them

Dr Grollman Dr Duncan you can explain this apparent paradox by the

fact that the mechanism of action following the two routes of administration is entirely different A large dose given parentally apparently acts peripherally whereas a small dose given orally acts through the organism s inability to replace serotonin in the brain an entirely different mechanism

DR MEILMAN I d like to question you Dr Grollman on that Do you really believe that this mechanism is through serotonin after what we ve seen indicating that only a small amount of reserpine accumulates in the nervous system? I think maybe Dr Plummer could answer this even better

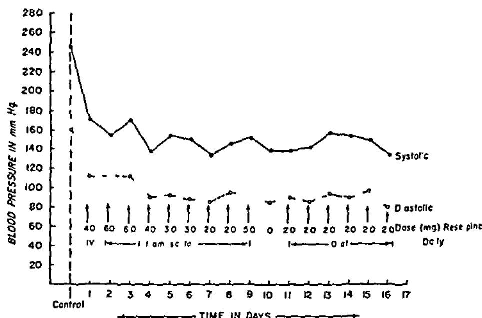


Fig 1 Blood pressure response during therapy with parenteral reserpine and after one week after conversion to the oral route The blood pressure was maintained quite consistently at normotensive or mild hypertensive levels Two weeks following discontinuation of parenteral reserpine pentolinium was added because of the gradual loss of adequate reduction in blood pressure (From Hughes *et al* A M A Arch Int Med 95 563 1955)

but I d like to know because I m not sure whether the central effect is a casual or a causal mechanism

DR PLUMMER As far as serotonin is concerned the evidences are indirect but nevertheless very persuasive I feel that the reserpine which we have been able to demonstrate in the brain for 48 to 72 hours after it was given does indicate that the action of reserpine does not have to be explained by a peripheral mechanism since reserpine itself is present in the brain As to the large dose given intravenously which Dr Grollman mentioned I m not sure that I agree with his statement because we get sedation in animals when we give them a large intravenous dose I just don t think that is a peripheral effect

DR DUNCAN This being a clinical aspect of the program I would like some member of the panel to tell us whether the reserpine given parenterally has a real place in the treatment of hypertensive crises when we can obtain such excellent results as we have just been shown when protoveratrine was used

DR HOOBLER You mean you want us to compare the effects of protovera trine and reserpine

DR DUNCAN Yes We want to know which drug would be used if a patient were admitted to the hospital in a hypertensive crisis

DR HOOBLER I would vote for parenteral reserpine every time because I think it is usually effective If it weren t effective after an hour or two I would be perfectly willing to try Dr Meilman s technique with protovera trine which I also have used and found effective but more troublesome because you have to be precise about the dosage whereas with reserpine you have a large therapeutic/toxic ratio

DR DUNCAN Recently we had a patient who was given 5 mg of reserpine parenterally which was ineffective when given repeatedly Protoveratrine was utilized with prompt reduction in blood pressure The emetic effects were reasonably well controlled even though they were a bit of a nuisance and frequent blood pressure determinations were required Until hearing Dr Hoobler talk about this my feeling was weighted very much in favor of protoveratrine given intravenously rather than parenteral reserpine Will some of the other members give their experiences?

DR MEILMAN I ll have to agree with what Dr Hoobler said If reserpine works it s a lot easier to use and certainly ought to be tried first And you'll know very soon if it s going to work When nothing has happened within one hour after intravenous reserpine then you can switch over to Veratrum But if reserpine does work your job of treating the patient is simplified

DR DUNCAN Any further comments on the subject?

DR MOYER There are some patients in a state of hypertensive emergency who do not respond to either parenterally administered reserpine or gangli onic blocking agents In my experience these patients will always respond to an intravenous infusion of Veratrum Figure 2 summarizes the course of such a patient who was treated with alkavervir (Veriloid) given in travenously

DR DUNCAN This takes us a little away from these two drugs but I would like to mention that in patients who have good renal function intravenous or oral doses of chlorothiazide will also take them over the hypertensive crisis We have followed eight patients who have had hypertensive en cephalopathy and most of these have been unable to take anything by mouth We ve given them intravenous chlorothiazide The results have been good in each instance and actually many of these people showed clinical improve

ment before their blood pressure fell I think it was simply a dehydrating effect of the diuretic It s a very simple method when renal function is all right

Dr Hoobler How about the blood pressure response?

Dr Kirkendall Actually the blood pressure response may not occur for some time as you know it may be a day or two before this occurs even longer at times We have seen clinical benefit within 2 to 4 hours even before the blood pressure decreased

Dr Meilman I would just like to make a brief comment about the rapidity of response when using protoveratrine for its hypotensive effect that is

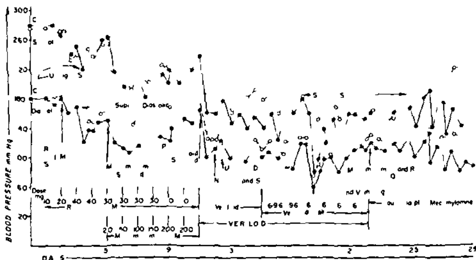


Fig 2 Blood pressure response to numerous agents given sequentially in a patient who initially was unresponsive to reserpine and ganglion blocking agents given intravenously Parenterally administered Veratrum was the most effective agent

10 to 20 minutes It is very unusual that this rapid effect is really necessary But *for example in hypertensive pulmonary edema a rapid onset of action* may be quite desirable I entirely agree with the reference to the claim made for the use of reserpine in emergencies but the onset of action after intravenous administration is not as prompt beginning perhaps an hour or somewhat longer after administration this compares to a delay of only 10 to 20 minutes after the parenteral administration of Veratrum

Dr Freis Since I don t know what the status of renal function is in most of the patients who come in with hypertensive emergencies I prefer to wait until I get a BUN before I get too enthusiastic about lowering their blood pressure drastically In a majority of the cases while you re waiting for the BUN intramuscular reserpine is very effective and seldom precipitates collapse in these people

Dr Hollander Even in the presence of convulsions you would not lower the blood pressure immediately?

Dr Freis Well at times you are forced to lower the blood pressure immediately but if you can wait and you dont know what the BUN is it is better to wait for the BUN

Dr Duncan It seems that the general impression of the panel is that the choice between these two drugs would be reserpine given parenterally to begin therapy

Dr Winer I would like to amplify some of Dr Meilmans comments with

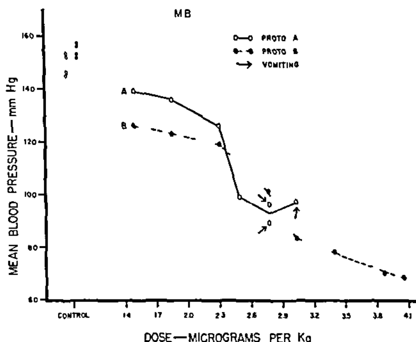


Fig 3 Comparison of the blood pressure response to protoveratrine A and protoveratrine B

reference to differences between single pure alkaloids I did a bioassay in humans and achieved many dose response curves of the type that Dr Meilman showed in his last slide (Fig 3) Protoveratrine B is slightly less potent mcg for mcg than protoveratrine A but it has a broader margin between the hypotensive and the emetic dose Since the problem in the use of Veratrum has been the narrow margin between the emetic dose and the hypotensive dose it would seem to me that for parenteral use protoveratrine B would be the Veratrum alkaloid of choice

Protoveratrine A and protoveratrine B are very different when given orally in that A is absorbed fairly well and B is absorbed poorly This actually means that when the mixture of protoveratrine A and B is used only the A is responsible for the response Consequently emesis is a serious handicap because of the narrow range between hypotensive and emetic activity I

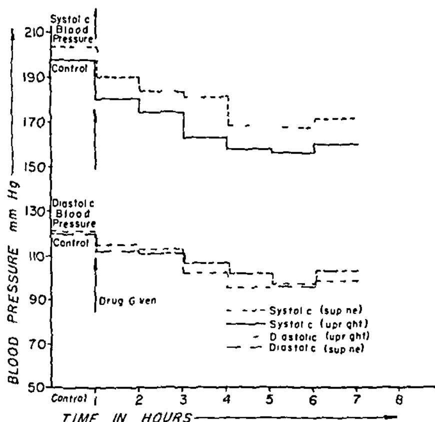


Fig 6 Graph of average values for 20 patients showing the upright and supine blood pressure responses to 10 mg of rescinnamine There was very little orthostatic effect similar to the response to reserpine (From Am J M Sc 231 542 1956)

is nearly the same when one uses a dose of rescinnamine which is double the dose of reserpine if the smallest doses producing maximum reduction in blood pressure are compared The blood pressure reduction in the supine position is just about as great as that observed in the standing position (Fig 6)

TABLE I INCIDENCE OF SIDE EFFECTS (OTHER THAN PSYCHIATRIC) WITH RESCINNAMINE AS COMPARED TO RESERPINE

	RESCINNAMINE		RESERPINE	
	NO	%	NO	%
Number of patients	84	100	62	100
Side effect				
Bradycrotic response	46	55	44	71
Sedation	29	35	29	47
Nasal congestion	43	51	40	65
Increased bowel movements	23	27	3	5
Increased appetite	26	31	37	60
Weight gain	28	33	31	50
Fatigue	34	40	27	44
Dizziness	13	15	13	21

When side effects other than the psychiatric ones are compared there is very little difference (Table 1) Therefore if the incidence of agitated depression is less in patients taking rescinnamine than in those taking *reserpine* as indicated by Dr Ford it should be logical to use either rescinnamine alseroxylon or the whole root (Raudixon) in those patients presenting this problem while taking reserpine

Dr Duncan Azotemia and uremia *in patients with hypertension is a* problem which faces many physicians Let's consider a patient with a BUN of 50 on the one hand and another patient with a BUN of 120 Do you care to comment Dr Freis?

Dr Freis I think that in either case the approach would be to lower the blood pressure much more cautiously and more gradually than you would do with the patient who does not have such severe impairment of renal function Also the therapist should follow the BUN very carefully drawing samples every 48 hours and watching to see whether the BUN rises as the blood pressure is reduced When the BUN rises as the blood pressure is reduced then the therapist should lighten up on his treatment a little—let the blood pressure get a little higher Subsequently the therapist should continue to try gradually but persistently to get the blood pressure down to reasonable levels instead of a period of a few days or a week this procedure may require several weeks This is even more important when the patient doesn't have a very high level of blood pressure So I would use chlorothiazide (Diuril) Rauwolfia and hydralazine (Apresoline) initially and even Veratrum if these others fail

Dr Duncan Did I understand you to say that you would use chlorothiazide?

Dr Freis Yes

Dr Duncan In the presence of azotemia?

Dr Freis Yes of the degree you mentioned

Dr. Duncan Any other comments on the use of sodium depletion with chlorothiazide in the presence of azotemia?

Dr Hoobler I would have an almost opposite recommendation I am very fearful of chlorothiazide in patients with azotemia Although I must admit that uremic symptoms have not often gotten worse when chlorothiazide was given I would prefer using ganglionic blocking agents in trying to lower the blood pressure in small increments The slow reduction in blood pressure is very important in these patients but on the other hand I think that we have lost patients because the residents were overcautious in this regard Let me present a hypothetical situation in which the BUN is 50 and the systolic blood pressure is 240 You lower the systolic blood pressure to 200 and 48 hours later the BUN goes up to 70 Most people would discontinue therapy and we have done so in such cases only to see the patient

die in uremia from progressive renal damage Sometimes when we continue therapy for another two days this temporary increase disappears and the BUN drops back to 50 again After you have achieved a reduction in blood pressure without a continuing increase in the BUN you might make another similar try several days later I point this out because everybody has become so apprehensive about the effect of the ganglion blockers on blood urea nitrogen that the least little rise in the BUN is interpreted as a signal to withdraw therapy The net result is that you have no other choice to offer than to let the patient die of uremia due to progressive renal damage

Dr Moyer The degree of blood pressure reduction is very important in these patients with severe renal damage due to hypertension When the kid

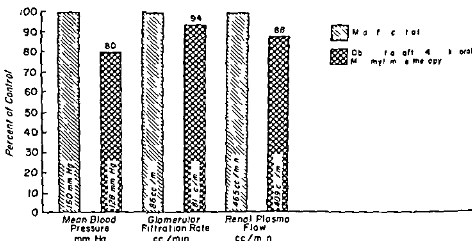


Fig 7 Renal hemodynamic response to chronic administration of mecamylamine given orally There was a slight reduction in glomerular filtration associated with a moderate reduction in mean blood pressure However this did not impair renal function significantly (From A M A Arch Int Med 98 187 1956)

neys are barely able to maintain adequate excretory function only a small reduction in glomerular filtration rate may completely decompensate the kidneys This is why slow reduction in blood pressure in small increments is so important under these circumstances In Figure 7 the renal hemodynamic response to a moderate reduction in blood pressure is shown There was very little depression in glomerular filtration rate In the patient presented in Figure 8 the blood pressure was dramatically reduced to 100/70 This response was associated with a rather marked depression in glomerular filtration rate Had renal damage been severe in this patient renal excretory failure would have ensued After renal hemodynamic readjustment occurs a greater decrease in blood pressure can be tolerated Should excessive blood pressure reduction occur at any time with cessation of renal function the process can be readily reversed by raising the blood pressure with any effective vasopressor agent (Fig 9)

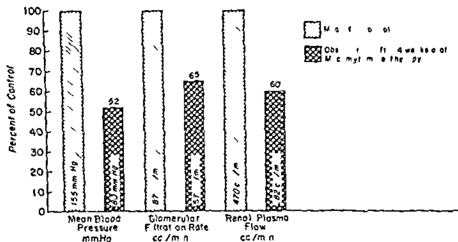


Fig 8 In this patient excessive reduction in blood pressure was produced by the administration of mecamylamine When this occurred there was a marked reduction in glomerular filtration rate This is of importance in the patient with severe renal damage since sudden reduction in glomerular filtration rate of this degree would decompensate the kidney (From A M A Arch Int Med 98 187 1956)

Fig 9 Excessive reduction in blood pressure resulted in severe depression in glomerular filtration rate and anuria. The untoward response was readily reversed by the intravenous infusion of norepinephrine

DR DUNCAN Do you use any alteration in the diet of these patients? I refer particularly to the reduction of protein let's say to 20 gm along with a liberal calorie allowance

DR HOOBLER Yes we would use dietary measures hydration etc in addition to blood pressure reduction

DR DUNCAN I suppose that I have been fanatical about the fact that if you deplete these patients of sodium you intensify the azotemia I have seen patients develop a more extensive degree of uremia in these circumstances I attributed it to the dehydrating effects of the sodium loss I am interested to know that Dr Freis gives a sodium depleting drug in the presence of azotemia

DR HOLLANDER We would be very cautious in the use of chlorothiazide in hypotensive patients with uremia Our experience has been similar to Dr Hoobler's Hypertensive patients with uremia when given chlorothiazide are particularly susceptible to further rises in the BUN and marked disturbance in the electrolytes may occur We certainly would not use chlorothiazide first in a hypertensive patient with uremia

DR FORD I will agree with both these folks but I think we may be neglecting a very valuable drug namely a saluretic agent such as a mercurial or chlorothiazide We are not talking about acetazoleamide (Diamox) *Diamox or any other carbonic anhydrase inhibitor is contraindicated in* uremia Here we are talking about chlorothiazide We may neglect to use this potent drug in certain patients just because they have an elevated blood urea nitrogen If we would like to take advantage of this drug it would be very simple to determine the 24 hour excretion of salt The patient can save his urine for 24 hours It can be done on an outpatient basis You can measure the amount of salt he takes in by giving him a diet containing 200 mg of salt and letting him add measured amounts of table salt which can be gotten at the drug store If he excretes more than 90 per cent of the intake in a 24 hour period then you should not give chlorothiazide On the other hand if he is retaining sodium I think we might give chlorothiazide

DR FREIS There is no denying that the BUN frequently does increase when you give chlorothiazide to azotemic patients I stand corrected on that point I was speaking however of individuals who have some congestive heart failure along with their hypertension Here some of the azotemia is due to the heart failure and in that type of individual I think chlorothiazide is helpful I would also remind you that the rice diet has been given for many years to people with severe impairment of renal function in azotemia and it too is a salt depleting regimen Yet many of these patients have done very well

DR DUNCAN I'm sure that many physicians would like to know what the ideal agents are for the management of hypertension in toxemia of pregnancy That has been touched on by Dr Meilman Would someone volunteer to answer this question?

DR MEILMAN I think that this is but one other example of hypertensive encephalopathy I would use Veratrum first but there have been some reports indicating that reserpine ought to be given initially There are also reports indicating that reserpine increases the number of seizures but it apparently doesn t increase the number of hypotensive seizures When the pressure comes down successfully the seizures are then controlled regardless of what drug has been used

DR DUNCAN Most articles on this subject give you the impression that hydralazine has a certain degree of specificity in these patients

DR MEILMAN I have used hydralazine a few times Sometimes it works very well Usually though one must be prepared for a pretty severe head ache when it is given to a patient intravenously Also hydralazine increases cardiac output Increase in cardiac output doesn t make much difference in the pregnant patient However we should not forget this fact because if we give it intravenously to a patient who has coronary artery disease we must anticipate real trouble

DR BRUST I think that there is considerable to be said in favor of Veratrum and Veratrum alkaloids in the management of preeclampsia and eclampsia It has been very well demonstrated that the hypertension associated with preeclampsia and eclampsia shows a remarkable specificity to this agent a much more remarkable specificity than does essential hypertension The use of this drug routinely in a hospital obstetrical practice has resulted in a significant lowering of maternal and infant mortality

DR DUNCAN Is there any member of the panel who would like to direct a question to Dr Hollander regarding iproniazid?

DR KIRKENDALL Yes I would It seems to me that at the 1958 Annual Meeting of the American Heart Association we heard that some monamine oxidase inhibitors caused loss of color vision Have you observed this?

DR HOLLANDER The compound that is reported to do this is the JB516 Our experience with the compound is limited and at the present time we have not observed this complication In general this compound appears to be better tolerated than iproniazid However it does cause a postural hypotension

DR MEILMAN I d like to ask if you ve seen severe psychiatric disturbance with iproniazid? I have in mind such symptoms as the patient forgetting her name and what day it was with relief in about three or four days after withdrawal of the drug Have you seen this in your series of cases?

DR HOLLANDER Yes in high doses that is doses of 150 mg a day we have observed abnormalities in behavior But on low dosage that is 25 to 50 mg a day this side effect is not common Occasionally some of the patients receiving this small dose may become anxious and extremely irritable but this is not common either It would appear that the patients who are over stimulated with the compound have a manic personality to begin with

DR MEILMAN It is customary to give pyridoxin with iproniazid Which of the side effects have you seen prevented by the administration of pyridoxin?

DR HOLLANDER We have not had any experience with pyridoxin However it is said to be helpful in those patients who develop neuralgia We had two patients who developed neuritis of the upper extremities on 150 mg of iproniazid given daily But on reducing the dosage the neuritis disappeared

DR MEILMAN I asked the question because we have been giving up to 50 mg of pyridoxin a day which is above the amount any person ought to require I haven t seen any of the toxic manifestations helped with pyridoxin and the toxic manifestations such as hyperflexia are just as severe

DR PATON I thought we ought to say something about the ganglionic action of iproniazid I m extremely doubtful whether it has any although this was suggested by Dr Hollander I haven t tested it directly on the classical test subject but Dr Bayne and I tried to establish such a response using the stimulated stomach and intestine which had ganglionic activity present The iproniazid did not interfere with the ganglionic transmission of impulses I think we would have noticed any ganglionic blocking action

DR HOLLANDER What do you think is the cause of the side effects of postural hypotension constipation dryness of the mouth occasional blurring of the vision and urinary difficulty? How would you explain these side effects?

DR PATON I don t know the cause but the arguments for its being ganglion blockade are not more powerful than for its being almost any of the other vasodilator effects or cholinergic blockade I wonder for instance if you re preserving some of the inhibitors of sympathetic amines in the body

DR MOYER We have used iproniazid in patients with angina pectoris who were not hypertensive It was ineffective Some patients even became worse In patients with hypertension and angina pectoris the drug was not nearly as effective in controlling the angina as Dr Hollander found to be the case in his patients

Clinical Use of Ganglion Blocking Agents in the Treatment of Hypertension and a Comparison of Different Blocking Agents

EDWARD D FREIS
Georgetown University School of Medicine

The ganglion blocking drugs are the most potent and reliable of all the agents used for reducing blood pressure but they also have the greatest variety and highest incidence of side reactions Skillful clinical management, therefore requires that the antihypertensive effectiveness be preserved or magnified and that the side effects be reduced to a minimum Various techniques are utilized to achieve this desired effect These will be discussed under the following headings (1) dosage adjustment (2) adjunctive therapy to enhance antihypertensive effects or combat opposing hypertensive influences and (3) measures to overcome side effects

DOSAGE ADJUSTMENT

Since the effective antihypertensive dose is highly variable from one patient to another it is mandatory to begin treatment at a low dosage and increase by increments to the effective level With the agents in general use today such as pentolinium tartrate (Ansolysen) mecamylamine (Inversine) and chlorisondamine (Ecolid) it is most convenient to give three doses per day at intervals as widely separated as is practicable Because postural hypotension generally is most severe in the morning I prefer to give the morning dose after rather than before breakfast The next dose is administered at 2 or 3 P M and the last at bedtime

In the early stages of therapy postural hypotension is more prominent than after prolonged treatment It seems probable that some degree of autonomous tone develops after several months of therapy Because of the pronounced postural effects initial dosage adjustments should be made on the basis of the blood pressure response in the erect position [1]

It is obvious that the blood pressure should be recorded frequently at least twice daily and preferably more often if one is dealing with severe resistant or malignant hypertension In the latter case the patient should be hospitalized during the initial period In cases of moderate hypertension therapy can be initiated on an ambulatory basis provided that the blood pressures are recorded at least twice daily in the home by the patient or a member of his family and that the other special measures discussed below are carried out

The frequency and magnitude of dosage elevations from the beginning to the effective level will vary somewhat according to individual circum

stances In a hospitalized patient it is possible to raise the dosage daily In ambulatory patients it is safer to proceed at a somewhat slower pace In general tolerable increments of dosage elevation are 50 per cent of the previous dose in the lower dosage range and 25 per cent in the higher

Complete flexibility and individualization of dosage adjustment are important in successful management The responsiveness of the patient varies with many factors including the time of day season of the year extracellular and plasma volumes drug tolerance and the patient s emotional state Much of this variability has been removed with the use of saluretic agents and "tranquilizer" drugs but for optimum results there still is a need for frequent recordings of blood pressure in many of the patients By this means it may be found that one of the doses is too small or too large or that the patient s reactivity has changed and a dosage modification can be initiated before any harm has been done

Inhibition of the autonomic nervous system blocks out moderating vasodilator as well as vasoconstrictor responses As a result the patient becomes more responsive to circulating epinephrine or norepinephrine Fear or anxiety promoting stimuli (but not anger or exercise) frequently produce overshoots of blood pressure If the pressure is recorded infrequently and especially by the doctor in his office or clinic considerable apprehension and anxiety may develop in the patient with a resulting overshoot of blood pressure The physician who relies only on office recordings will fail in a high percentage of his patients because he will overdose on the basis of misleadingly high and unrepresentative readings Severe hypotension and other side effects then will occur and he will conclude that satisfactory dosage regulation is not possible

Another advantage of home recordings is that they add to the patient s understanding of the therapeutic program and increase his cooperation When he forgets or deliberately omits dosages he sees for himself the harm ful results in his blood pressure levels With such persuasion he is more tolerant of side effects than he would be otherwise As treatment progresses and if satisfactory blood pressure control is achieved the frequency of home recordings can be reduced to once or twice per week The notion that home recording makes the patient unduly apprehensive or neurotic has been found to be untrue in actual clinical practice For the physician there is no better way to gain an intimate knowledge of the clinical effects of anti hypertensive agents than by this method

ADJUNCTIVE THERAPY TO ENHANCE ANTIHYPERTENSIVE EFFECTS AND OPPOSE HYPERTENSIVE INFLUENCES

The introduction of chlorothiazide has greatly facilitated the manage ment of the patient taking ganglion blocking drugs Many who required these agents in the past now can be controlled adequately with chlorothiazide and small dosages of hydralazine [3] In others the dosage of the blocking agent can be reduced to the point where side effects become minimal [4]

The combined effects of chlorothiazide and ganglion blockers are truly synergistic After reducing plasma volume with chlorothiazide only a mini mal degree of sympathetic inhibition is required to reduce central venous pressure and hence cardiac output (see paper in Part I on Observations

on Cardiac Output Peripheral Blood Flow and Blood Volume in Hypertension—Before and During Treatment)

The increase in peripheral vascular capacity combined with the decrease in plasma volume is bound to have a most potent effect on venous return For this reason it is mandatory that if chlorothiazide is added to the regimen of a patient on ganglion blocking agents the dosages of the latter must be reduced in half at the time that chlorothiazide is begun

A dose of 500 mg of chlorothiazide twice daily is sufficient and the usual precautions should be taken in regard to potassium depletion (see paper in Part IV on Clinical Pharmacology and Use of Chlorothiazide in the Treatment of Hypertension) If cholorothiazide is begun first and the ganglion blocker is added later beginning dosages of the blocking drug may be as follows for pentolinium tartrate and chlorisondamine 10 mg three times daily and for mecamylamine 1 25 mg Dosages usually can be increased substantially from this level

There are some patients with moderately severe hypertension who require ganglionic blocking agents in order to obtain an initial reduction of blood pressure After several months of treatment however it is then possible to substitute hydralazine in small dosage (75 to 150 mg per day) with continued control of the blood pressure In other words more drastic measures sometimes are required to obtain initial control but following this period less potent medications often are able to maintain the antihypertensive effect

It has been mentioned that fear and anxiety may overcome the antihypertensive action of the ganglion blocking drugs For this reason the so called tranquilizing agents aid in smoothing out the peaks and valleys of the blood pressure chart characteristic of the hypertensive who is treated with ganglion blocking drugs and no other adjunctive therapy The most effective tranquilizer is reserpine but it is also the most dangerous because of the frequency of depressions Phenobarbital Sodium Amytal or meprobamate should be tried first followed by reserpine only if necessary The maintenance dose of reserpine should be kept as low as possible generally 0 25 mg per day The patient also should be warned about the possibility of developing a depression so that the drug can be withdrawn without delay if this complication should occur

MEASURES TO OVERCOME SIDE EFFECTS

Since the ganglionic blocking agents inhibit transmission through all autonomic ganglia parasympathetic as well as sympathetic the side effects can be numerous and diverse If the measures already outlined are observed the incidence of side effects should be low and their severity much reduced In general they will be most troublesome in the patients with malignant hypertension who often require more complete degrees of ganglionic blockade

One of the most common side effects is constipation This was much more frequent and severe prior to the chlorothiazide era Ordinarily laxatives such as magnesium hydroxide and Cascara sagrada taken at bedtime are sufficient If necessary neostigmine (Prostigmin) in a dose of 15 to 30 mg can be taken orally on arising The dosage of neostigmine must be titrated

to avoid explosive diarrhea tremors and sweating In stubborn cases especially early in treatment Fleet s enemas may be required In severe hypertensives if care is not taken to assure daily bowel movements during the first few weeks of therapy paralytic ileus can occur

Paralysis of visual accommodation is another common side effect Patients suffering from this complaint should wear dark glasses in bright sunlight and reading glasses for adjusting to near vision Since the degree of impaired visual accommodation fluctuates and often is only a transient phenomenon it usually is not necessary to send the patient to an ophthalmologist for a fitting Quite often at the time of the appointment visual accommodation is not impaired and the patient comes away with a useless and expensive pair of spectacles A more satisfactory solution is to advise the patient to visit a local variety store when his near vision is blurred and try on glasses of different strengths until he finds a pair which restores his ability to read fine print

Failure of salivary secretion resulting in dry mouth may be troublesome at times Pilocarpine nitrate given in a 5 mg tablet one half hour before meals sometimes is helpful but tends to lose its effectiveness if it is administered frequently When dry mouth is severe switching to another blocking drug sometimes is helpful Occasionally the dosage of the blocker must be reduced In such cases reserpine hydralazine and chlorothiazide all should be tried in combination in the attempt to achieve the best possible blood pressure control Perhaps the monamine oxidase inhibitors can be used to advantage in such cases

The patient should be told that because of dilation of skin blood vessels he will lose body heat when exposed to a cold environment He should therefore dress more warmly than is his custom in order to avoid chilling when he proceeds out of doors on a cold day

There are other side reactions for which no effective countermeasures are available except reduction in the dosage or omission of the blocking agent Such side effects include impotence delayed and difficult micturition distaste for certain foods bloating after meals and severe postural hypotension

It is helpful to discuss some of the expected side effects and their prevention with the patient at the time that therapy is initiated so that he will not become unduly alarmed when and if a reaction occurs Such counsel may aid also in the prevention of disturbing reactions For example the hospitalized patient should be told to sit on the side of the bed for a few moments before arising and if he feels faint or dizzy not to stand up but rather to lie down again He should be advised to remain standing beside the bed for a minute before moving away to test himself for postural faintness This is important in the early dosage adjustment phase of treatment.

Constipation also should be discussed and the patient advised to be particularly insistent with the nurses in regard to his need if any for laxatives It is better not to discuss with him certain other side effects such as impotence since you may discourage him before the desired antihypertensive effect has been achieved After the blood pressure has been successfully reduced it is easier to convince him that the price he has to pay for blood pressure control is not too high

There is very little to choose between the various blocking agents in actual clinical practice Mecamylamine being a secondary amine (*it is not*

a ganglionic blocker in the strict sense[*]) possesses the advantage of complete intestinal absorption Although this tends to produce fewer fluctuations in the blood pressure it should be remembered that other influences play an important part in altering the patient s responsiveness These latter factors as well as variations in absorption combine to produce the fluctuations in blood pressure In actual practice chlorothiazide by maintaining a constant reduction in extracellular fluid volumes and the tranquilizers by allaying anxiety have done more to smooth out the fluctuations than has mecamylamine alone

In some individuals mecamylamine has the disadvantage of producing a more intense degree of parasympathetic blockade If the patient who takes this drug complains of difficulty in emptying the urinary bladder or resistant constipation or severe dry mouth it is advisable to shift to another blocking agent In cases with renal failure mecamylamine may produce tremors and other neurologic aberrations On the other hand if a patient exhibits considerable fluctuations of blood pressure on another blocking drug mecamylamine can be tried and often is helpful

Pentolinium tartrate (Ansolysen) is a ganglion blocking drug of the classic type Only about 5 per cent of an oral dose is absorbed However it is quite reliable and there has been a relatively long experience with this drug There are no toxic reactions other than those associated with ganglionic blockade

Chlorisondamine (Ecolid) is an asymmetric quaternary ammonium salt There is some evidence to suggest that these types of compounds have a central as well as a ganglionic blocking component[6] This may explain why the drug appears to have more effect on visual accommodation and perhaps slightly less constipating effect than the others previously mentioned

There are many other ganglion blocking drugs in the process of clinical evaluation Slight differences in duration of action incidence of side effects and drug tolerance have been noted As yet none of these developments represent an important therapeutic breakthrough However since the ganglion blocking agents have proved their worth a continued search seems justified

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Newer Ganglion Blocking Agents Comparative Observations

S W HOOBLER J S CONWAY and P BLAQUIER
University of Michigan Medical School

The first report of the use of a ganglion blocking agent in the human subject appeared only 12 years ago[1] The pharmaceutical industry has produced many chemical relatives of this first drug tetraethyl ammonium and with the discovery of a completely absorbed ganglion blocking agent of different structure mecamylamine many of us felt that the end was in sight for this particular family of drugs However it is a pleasure to report here on some offspring of the second generation of these drugs which have not turned out so badly after all

Thanks to the efficacy of background therapy with chlorothiazide it is not necessary to give such large doses of ganglion blocking drugs as formerly We may turn our attention to reducing the degree of parasympathetic blockade and to drugs with a longer or shorter action span

My colleagues and I have studied trimethidinium methosulphate (Ostensin) in this connection This quaternary blocking agent is said to be well absorbed and to have a long acting effect in animals[2] and in man[3] Our experience[4] has confirmed its striking and prolonged hypotensive effect when injected intravenously (Fig 1) Furthermore we have substituted trimethidinium for mecamylamine in patients with severe hypertension who were also receiving chlorothiazide The patients took their own blood pressure and were instructed to increase the dose of the new drug gradually until the standing blood pressure reached the levels achieved with mecamylamine therapy At this point the frequency of side effects was reviewed Table 1 presents our findings which indicate that constipation was considerably improved and that blurring of vision was more prominent All gastrointestinal side effects of blockade with mecamylamine including flatulence and dry mouth were improved Perhaps because of its relative lack of interference with gastrointestinal motility we found that blood pressure control remained well stabilized on the new drug However it has the disadvantage that by the oral route incomplete absorption occurs as with other quaternary ammonium compounds One patient whose blood pressure had been controlled at a quite constant level took several doses of paregoric to stop a temporary diarrhea there was a striking fall in blood pressure levels for several days until the paregoric was discontinued

Most patients particularly in the younger age groups noted that blurring of vision became more prominent One individual said that the effects of the new drug on the vision resembled those produced by chlorisondamine (Ecolid)

The orthostatic blood pressure gradient and the occurrence of impotence were about equal with the two drugs We found no evidence of tolerance developing over a one to eight month period It was our impression that

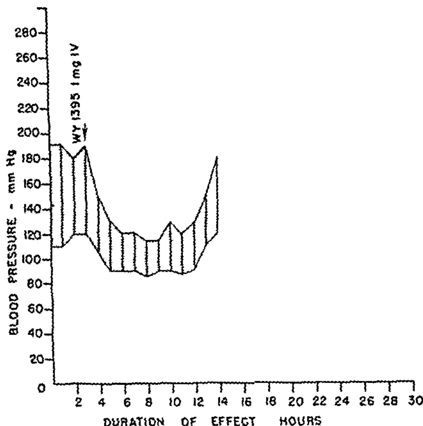


Fig 1 Effect of 1 mg trimethidinium on the blood pressure in hypertension

TABLE I COMPARATIVE EFFECT OF INVERSINE AND OSTENSIN ON BLOOD PRESSURE AND PARASYMPATHETIC SIDE EFFECTS

	BLOOD PRESSURE (mm Hg)		DAILY DOSE (mg)		SIDE EFFECTS BEFORE AND AFTER RX (Severity Grade)			
					Vision		Constipation	
AGE	Inversine	Ostensin	Ins	Ost	Ins	Ost	Ins	Ost
53	100/80	1[illegible]0 90	45	100	0	0	1	0
49	134/90	140/90	[illegible]	20	0	1	1	0
34	140 90	155 4[illegible]	20	180	0	3	2	0
6[illegible]	165/100	120/9[illegible]	10	40	0	0	0	0
2[illegible]	148/102	160/118	[illegible]0	120	2	1	3	1
58	1[illegible]2/118	160/103	22	60	0	1	3	1
[illegible]	150/96	114/88	25	20	0	0	0	0

Mean of twice daily standing blood pressures recorded by the patient during the last week of the therapeutic period. The dosage of each drug was adjusted by the patient to achieve equal blood pressure reduction on the two regimens. Ratio of dosage to achieve equal antihypertensive effect varied widely. Chlorothiazide 500 mg twice daily was also given to all patients in the study. Ostensin reduced constipation but visual blurring worsened.

when large doses of mecamylamine were required to treat severe hypertension conversion to trimethidinium was rarely successful However when in addition to chlorothiazide and a low salt regimen the mecamylamine requirement was minimal or the desired blood pressure reduction was not great the use of trimethidinium was frequently successful and could be carried through with fewer unpleasant side effects

We used approximately the same dosage schedule in converting patients from mecamylamine to trimethidinium (outlined in Table 2) for the initiation of treatment with this agent Because mecamylamine is slowly excreted the final dosage of trimethidinium may take longer to establish than when no other ganglion blocking agent has been given

TABLE 2 TREATMENT OF HYPERTENSION WITH OSTENSIN RECOMMENDED DOSAGE SCHEDULE

Preparatory	Salt depletion with low salt diet plus chlorothiazide 0 5 gm twice daily
Initial	20 to 40 mg twice daily before meals Prescribe daily laxatives
Maintenance	Increase by 20 mg in A M and P M daily (hospital) or every three days (home blood pressures) until desired standing blood pressure reached

Trimethidinium is an interesting offspring of a distinguished family of quaternary drugs including hexamethonium pentolinium chlorisondamine and a host of others less well studied It inherits the parents inability to pass completely through the gastrointestinal wall but it seems to have improved on the older generation by producing less inhibition of gastric motility

Tertiary amines are relatively new comers to the field They are a much admired family because of their dependability of absorption There is a new offspring of this family pempidine[5] which is said to differ from the parent compound in having a shorter duration of action Harington Kincaid Smith and Milne[6] have compared the drug with mecamylamine and find less plasma protein binding more rapid excretion and less dependence for renal elimination upon urinary pH They report that 60 per cent of the maintenance dose of mecamylamine is necessary with pempidine but that it is best administered in four equal daily doses to achieve a smoother action A dose of 2 5 mg four times daily is recommended at the commencement of therapy with a rapid build up permitted by the more rapid excretion of the new compound On the basis of a very brief experience with the drug we have noted that such a starting dose is almost too effective and that 2 5 mg twice a day is safer to begin treatment Our preliminary experience would suggest that side effects are at least as prominent as with mecamylamine and that the alleged need for frequent administration may represent a disadvantage except in cases where a brief vacation from therapy may be desired as when impotence or severe constipation with flatulence is to be avoided

A new derivative with a much longer duration of action has been reported by our British colleagues[7] This agent pentacynium appears to have an even more prolonged action than mecamylamine Depending on your point of view this can be considered an advantage or a disadvantage for a new drug The history of pharmacology is replete with instances in which long acting agents replace shorter acting ones If the new drug which we have

not yet had the opportunity to study is nontoxic and does not cause more side effects per unit of blood pressure reduction than the conventional blocking agents I suspect it will be readily accepted into the ganglion blocking family by hypertension therapists and their patients

SUMMARY AND CONCLUSION

Recently developed ganglion blocking agents give promise of some reduction in gastrointestinal side effects (trimethidinium) and some reduction in persistence of action (pempidine) The management of severe hypertension may be improved by the use of these drugs in severe cases Further experience is necessary before their place in the therapeutics of hypertension is finally established

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Beneficial Results Derived from and Problems Associated with the use of Ganglionic Blocking Agents

RALPH V FORD

Baylor University College of Medicine

BASIC CONSIDERATIONS OF GANGLIONIC BLOCKADE

Causative factors in the development of hypertension are numerous however one common denominator in the hypertensive state appears to be sympathetic predominance of the vasoconstrictor mechanisms responsible for maintaining arterial blood pressure Today there are available a number

of therapeutic agents that are capable of lowering the blood pressure by blocking the flow of impulses over the sympathetic component of the autonomic nervous system These agents are still the most effective anti hypertensive agents available to the clinician

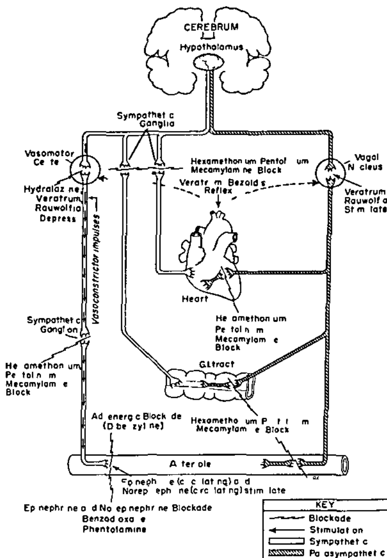


Fig 1 Pharmacology of antihypertensive drugs One is caught between the Scylla of hypertension due to excessive sympathetic activity (or increased vascular responsiveness) and the Charybdis of excessive parasympathetic blockade (From A M.A Arch Int Med 98 187 1956)

If overactivity of the sympathetic nervous system or increased responsiveness of the arteriole is important in the pathogenesis of hypertension its blockade by chemotherapeutic means will be attended by certain unnatural physiologic events Since the ganglionic blocking agents as we com

monly know them are actually autonomic ganglion blocking agents it is to be expected that the most unnatural events will be due to blockade of the parasympathetic ganglia This general concept may be illustrated in Figure 1 It should be obvious therefore that in the use of ganglionic blocking agents one is caught between the Scylla of hypertension due to excessive sympathetic activity and the Charybdis of excessive parasympathetic blockade

METHODS OF DETERMINING BENEFITS OF GANGLIONIC BLOCKADE

There are at least two methods of determining that ganglionic blockade is beneficial in the chemotherapy of hypertension The first may be labeled the "eyeball approach"—i e we *see* patients with severe hypertension who are living today who would be dead had they not received this treatment The second approach may be labeled the physiologic approach—i e discrete observations of reversal of organ deterioration following ganglionic blocking therapy

The data in Table 1 are representative of a small segment of our hypertensive population and suggest that active treatment with ganglionic blocking agents may be of value if one is merely interested in the eyeball approach The difference in mortality between patients with malignant hypertension who receive treatment and those who do not is highly significant

TABLE 1

FOLLOW UP IN THIRTY-ONE PATIENTS WITH MALIGNANT HYPERTENSION

Cause of Death	Treated Patients*	Untreated Patients†
No of patients observed	13	18
Cerebrovascular accident	1	3
Cerebrovascular accident + uremia	1	1
Uremia	0	11
Cardiac	0	2
Average survival time (mo) or follow up period if living	30	14

* Thirteen patients treated eleven living two dead
† Eighteen patients untreated one living seventeen dead

However if one needs more objective data to support the thesis that ganglionic blockade is beneficial in hypertension it is necessary to consider changes in various organ systems Most of our work has been focused upon changes in the vascular bed of the kidney but we feel that these observed changes are a reflection of beneficial changes in other important vascular beds viz brain and heart

BENEFICIAL RESULTS OF GANGLIONIC BLOCKADE

Although effective reduction of the blood pressure in patients with hypertension can be readily accomplished with the use of rather recently developed drugs the effectiveness of blood pressure reduction in arresting the vascular injury associated with hypertension had not been previously proved We have recently completed an analysis of patients with hypertensive vascular disease in which the renal functional status of the patients was determined by means of clearance tests [1] Results of the analysis were in agreement with those previously reported by others demonstrating that patients

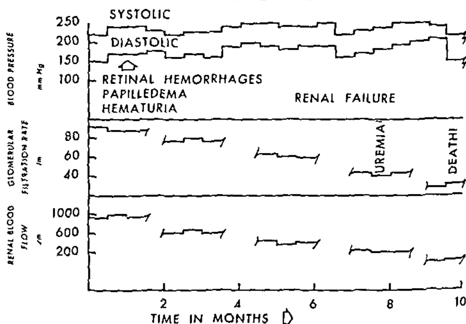


Fig 2 Progressive vascular deterioration observed in a patient with malignant hypertension who was not treated (*From Am J Med 24 177 1958*)

with hypertension have a significant reduction in glomerular filtration rate and renal blood flow which is proportional to the severity and duration of the sustained blood pressure elevation

Clinical observations made on a few patients with malignant hypertension (Figs 2 and 3) suggested that renal vascular deterioration was progressive and that blood pressure reduction was of some value in arresting the renal deterioration that occurs in patients with this disease Additional studies in a larger group of hypertensive patients of varying degrees revealed similar results The results clearly demonstrate the value of effective treatment of hypertension in arresting renal vascular deterioration associated with this disease

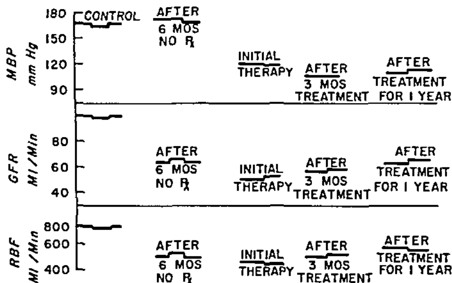


Fig 3 Patient with malignant hypertension showing progressive renal vascular deterioration over a period of six months without treatment Following blood pressure reduction with Rauwolfia in combination with a ganglionic blocking agent (mecamyl amine) the vascular deterioration was arrested but did not return to normal after a period of one year (From Am J Med 24 177 1958)

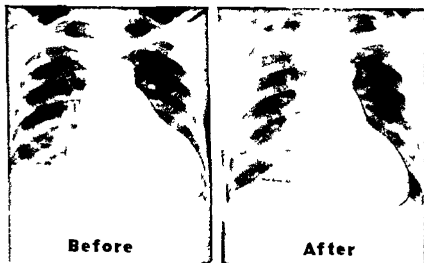


Fig 4 Associated with the reduction in blood pressure in this patient with malig nant hypertension there was a definite decrease in the size of the heart This occurred with no therapy other than blood pressure reduction (From Am J Med., 24 177 1958)

Since it has been demonstrated that deterioration of renal function can be arrested by treatment in severe cases it seems only reasonable to suppose that early treatment of the mild and moderately severe case would be of even greater value in delaying or preventing the vascular deterioration in the kidney The slow nature of the disease process in these patients can be used to advantage by the clinician for it is in this type of patient that the blood pressure can be reduced gradually and much more effectively over a longer period of time thereby preventing some of the untoward reactions to rapid reduction of the blood pressure Finally there is evidence to indicate that improvement occurs in the electrocardiogram associated with a de-

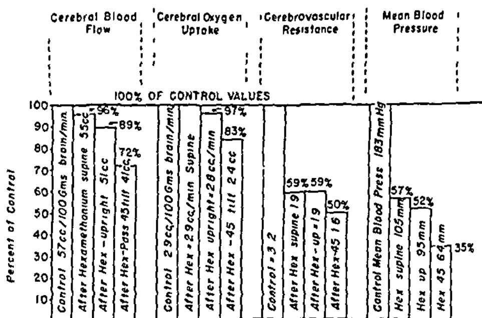


Fig 5 Cerebral hemodynamic response to blood pressure reduction with hexamethonium in a patient with malignant hypertension The effect of reduction in blood pressure in the supine position is contrasted with that in the upright position accompanied by active motion of the legs and that in a 45 degree head up position with passive tilting (From J A M A 152 1121 1953)

crease in heart size of the treated patients (Fig 4) not only in those with severe hypertension but in patients with mild hypertension as well These data will be presented in greater detail by another participant in this symposium Dr Charles Heider[3]

That these data are a reflection of beneficial changes occurring in other vascular beds is illustrated by Figure 5 which describes the decrease in cerebral vascular resistance accompanying the reduction in blood pressure by a ganglionic blocking agent hexamethonium Further changes in the fundi of hypertensive patients are frequently very striking following effective ganglionic blocking therapy of severe hypertension (Fig 6)

The beneficial effects of ganglionic blocking therapy are summarized

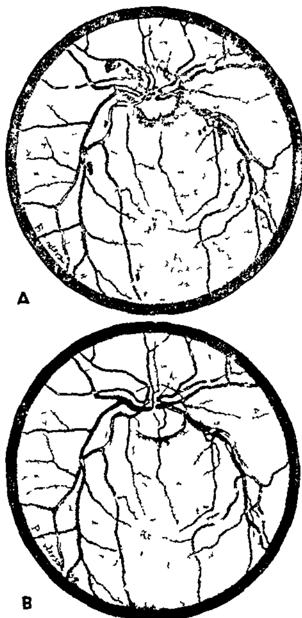


Fig 6 A funduscopic changes in patient G L M prior to antihypertensive therapy B funduscopic changes following antihypertensive therapy for a period of one month (From Am J Med 24 177 1958)

in Table 2 which presents our experience with mecamylamine (Inversine) alone (50 patients) and in combination with Rauwolfia (200 patients) These data indicate that vascular deterioration in the brain heart and kidneys can be effectively retarded by appropriate therapy viz sympathetic depressants Probably the most dramatic clinical improvement is seen in the

amelioration of congestive heart failure in the patient with hypertension after control by the use of ganglionic blocking agents (Table 2)

TABLE 2 BENEFICIAL EFFECTS OF MECAMYLAMINE ALONE COMPARED WITH MECAMYLAMINE PLUS RAUWOLFIA

	MECAMYLAMINE ALONE	MECAMYLAMINE & RAUWOLFIA
	% OF PATIENTS COMPLAINING	
Bradycardia induced	13	50
Headache	54	71
Angina	91	100
Retinopathy	52	72
Congestive heart failure	63	81
Renal impairment	13	25
Abnormal ECG	13	26
(Total number of patients	50	200)

ADVERSE EFFECTS OF GANGLIONIC BLOCKING THERAPY IN HYPERTENSION

When a chemotherapeutic agent produces ganglionic blockade it blocks the parasympathetic as well as the sympathetic ganglions Most of the side effects associated with the reduction in blood pressure can be attributed to the curare like effect (weakness and fatigue) parasympathetic ganglionic blockade (constipation urinary retention dry mouth and anorexia) or excessive hypotension (dizziness and syncope) which is predominantly orthostatic The frequency of these reactions of an adverse nature is depicted in Table 3

TABLE 3 SIDE EFFECTS OF MECAMYLAMINE ALONE COMPARED WITH EFFECTS OF MECAMYLAMINE WITH RAUWOLFIA

	MECAMYLAMINE ALONE % OF TOTAL	MECAMYLAMINE & RAUWOLFIA % OF TOTAL
Sympathetic blockade		
Syncope	4	5
Parasympathetic blockade		
Anorexia nausea or vomiting	33	11
Constipation	79	69
Cycloplegia	54	43
Dry mouth	67	41
Impotence	50	60
Bladder atony	4	5
Curare like weakness	67	46
(Total number of patients	50	200)

Other more esoteric adverse effects may be noted When blood pressure is reduced the cerebral vessels dilate and cerebral blood flow and cerebral metabolism are maintained however if the pressure is reduced excessively cerebral blood flow decreases and disturbances in cerebral function follow This is more likely to occur in the upright position especially if not accompanied by muscular activity If cerebral ischemia is to be avoided while the patient is standing the blood pressure should be adjusted with the patient in the upright position Reduction in blood pressure in the supine position

has no significant effect on cerebral blood flow or cerebral oxygen uptake because of the reduction in cerebrovascular resistance a result of cerebral arteriolar dilation In the upright position there is a slight reduction in cerebral blood flow Passive head up tilt should be undertaken with extreme caution in these patients

Following acute blood pressure reduction with ganglionic blockade (studies in supine position) there is an initial depression of renal function Glomerular filtration gradually returns to normal however despite a maintained reduction in blood pressure provided the reduction is not excessive The patient whose course is shown in Figure 7 was admitted to the hospital

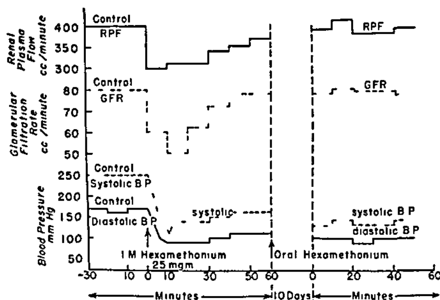


Fig 7 Acute response of blood pressure and renal function to intramuscularly administered hexamethonium and their status 10 days later during maintenance therapy with orally administered hexamethonium (From J A M A 152 1121 1953)

in a semi comatose state associated with a hypertensive crisis The blood pressure was reduced acutely with parenterally administered hexamethonium and renal functions (glomerular filtration rate and renal plasma flow) were depressed as the blood pressure decreased Despite maintenance of the reduction in blood pressure renal function returned to normal The patient was later given the drug orally and although blood pressure was maintained at 130 mm Hg systolic and 100 mm Hg diastolic renal function was not depressed in comparison with the initial treatment levels

Patients with renal damage respond to blood pressure reduction qualitatively similarly to patients with normal kidneys but the readjustment is slower A few patients fail to readjust completely to a lowered blood pressure If readjustment is incomplete there is little need for concern if renal function is relatively normal however if renal function is severely impaired even small reductions in glomerular filtration may seriously decompensate the excretory capacity of the kidney Therefore in the presence of impaired renal function the therapist must be alert to this possibility

In summary the majority of the side reactions are the result of both

sympathetic and parasympathetic blockade and are qualitatively similar in all ganglionic blocking agents These reactions are to be expected when the drugs are used The incidence of these side reactions however can be minimized and the beneficial effects increased by the judicious regulation of dosage particularly when the drugs are used in combination with diuretic agents and with centrally acting drugs such as the Rauwolfia extracts Time and space do not permit consideration of some of the more rare reactions to ganglionic blocking agents such as the pulmonary and neurologic syndromes reported by some observers

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Comparison of Blood Pressure Responses and Symptomatic Effects of Mecamylamine and Currently Available Quaternary Ammonium Compounds

JOHN H MOYER
Hahnemann Medical College and Hospital

Ford[1] has reported that the beneficial effects derived from the use of ganglionic blocking are approximately the same irrespective of the blocking agent being given It seems to me that this should be emphasized since it is the reduction in blood pressure that is important in therapy Although the newer blocking agents such as mecamylamine (Inversine) which have become available are easier to use and the dose adjustment is more simple the therapeutic results are approximately the same as those obtained with the use of hexamethonium administered by the oral route

Table 1 is taken from a paper published in 1953[2] showing the symptomatic improvement observed immediately after the establishment of an effective reduction in blood pressure with hexamethonium in patients with hypertension and a comparison with the effects observed three months later

TABLE 1 SYMPTOMS RELIEVED OR IMPROVED BY HEXAMETHONIUM CHLORIDE

SYMPTOMS OR SIGNS	NO WITH COMPLAINT	NUMBER IMPROVED INITIALLY NO	%	3 MONTHS NO	%
Headache	22	18	82	16	73
Albuminuria	16	9	56	13	81
Precordial pain	14	7	50	11	79
Retinopathy†	21†	9†	43	16†	76
Hematuria	8	4	50	7	88
Heart failure	16	8	50	13	81
Nervous tension	16	11	69	14	88
EKG					
Left vent strain	22	5	23	16	73
Myocardial damage	24	1	4	5	21

Headaches following the onset of hypertension
† Includes only those patients with retinopathy of grade III and IV

Follow up studies after three to five years now indicate a continuation in the improvement of the symptoms associated with hypertensive vascular disease when the blood pressure was reduced with ganglionic blocking agents

In Table 2 the response rates of four different ganglionic blocking agents given in combination with Rauwolfia are compared A response rate is defined as a reduction in mean arterial blood pressure of 20 mm Hg or more or a return to normotensive levels Normotensive levels were considered to be below 150/100 Although the response rate was somewhat higher with mecamylamine than with the other blocking agents the difference was not great and probably reflects a difference in the vigor of the therapeutic approach rather than real differences between the results that could have been obtained had maximum amounts of the drug been administered in each instance The greatest difference is in the potency of the different drugs and the ease of administration Since mecamylamine is completely absorbed from the gastrointestinal tract it is easier to give and the response is more predictable Also greater experience with these compounds improves the ability of the therapist to use them in a more effective manner Since mecamylamine is completely absorbed the dose administered intravenously and the dose requirement by the oral route are the same This has some

TABLE 2 COMPARISON OF BLOOD PRESSURE RESPONSE (UPRIGHT) WITH DIFFERENT GANGLIONIC BLOCKING AGENTS COMBINED WITH RAUWOLFIA

	RAUWOLFIA + MECAMYLAMINE (Inversine)	+ HEXAMETHONIUM	+ PENTOLINIUM (Ansolysen)	+ CHLORISONDAMINE (Ecolid)
No patients treated	80	75	75	44
Responsive	94 per cent	76 per cent	79 per cent	80 per cent
Normotensive	38 per cent	37 per cent	33 per cent	3[illegible] per cent
Unresponsive	6 per cent	24 per cent	21 per cent	20 per cent
Average 24 hour dose of responsive patients	25 mg	2307 mg	341 mg	253 mg

advantage when converting from the parenteral route of administration to the oral route

There are quantitative differences among the various ganglionic blocking agents For example dryness of the mouth and constipation are more frequent and the severity is greater following the administration of mecamylamine than following the other compounds Although constipation is less marked with chlorisondamine (Ecolid) than with mecamylamine and pentolinium photophobia is more severe in these patients In fact blurring of vision and photophobia are serious drawbacks to the use of this compound particularly in patients who do a lot of paper work and who depend on their eyes for their occupation

Ford[1] has shown that Rauwolfia given concurrently decreases the incidence and severity of many of the side effects associated with the use of the ganglionic blocking agents This is due in part to the fact that Rauwolfia depresses the sympathetic nervous system in the brain at the same time that the ganglionic blocking agents block impulses at the ganglia The concurrent use of Rauwolfia with ganglionic blocking agents decreases the dose requirement of the ganglionic blocking agents and consequently the side effects It also appears that the Rauwolfia compounds make the blood pressure response more stable perhaps by decreasing the patient s responsiveness to his environment The Rauwolfia compounds alone however are not adequately potent and therefore in patients with severe hypertension the ganglionic blocking agents and/or chlorothiazide must be given in addition to Rauwolfia

TABLE 3 SOME SYMPTOMS AND THE BENEFICIAL EFFECT OF ANTIHYPERTENSIVE THERAPY (FIGURES = PER CENT IMPROVED)

SYMPTOMS	RAUWOLFIA ALONE	RAUWOLFIA + PENTOLINIUM	RAUWOLFIA + MECAMYLAMINE
Number of patients treated	346	75	80
Bradycrotic response	65	67	49
Headache	70	78	71
Angina pectoris	38	71	80
Congestive heart failure	16	65	81
Electrocardiographic abnormality	7	40	25
Renal damage	0	37	25
Funduscopic changes	5	58	59
Cardiomegaly (x ray)	20	52	31

A decrease in the pulse rate of 10 beats per minute or more

Table 3 compares the clinical response in a group of patients receiving Rauwolfia alone and in combination with pentolinium or mecamylamine It is quite obvious that the response to the combination of Rauwolfia and a blocking agent is much better than the response to Rauwolfia alone Contrariwise there is very little difference in clinical response comparing pentolinium and mecamylamine given in combination with Rauwolfia

One aspect of therapy that has not been emphasized as yet is the treatment of fulminating heart failure which is sometimes seen in association with severe hypertension Here the ganglionic blocking agents are the most effective therapeutic agents (Table 4) These should be given in addition to the usual treatment for heart failure which includes digitalis and diuretics

The ganglionic blocking agents in addition to reducing the blood pressure also reduce the venous pressure and consequently the venous return to the heart As Freis[3] has pointed out this leads to an increase in cardiac output and consequently to an improvement in symptoms due to the heart failure At the same time there is a sharp reduction in pulmonary pressure and in pulmonary edema

TABLE 4 SUMMARY OF RESULTS IN PATIENTS TREATED WITH GANGLIONIC BLOCKING AGENTS FOR FULMINATING HEART FAILURE ASSOCIATED WITH SEVERE HYPERTENSION

	HEXAMETHONIUM	MECAMYLAMINE (Inversine)	ARFONAD
Number patients treated	16	8	11
Significant reduction in blood pressure	12	6	10
Normotensive	4	2	9
Improvement in pulmonary edema	13	7	10
Recovery	12	6	10

We have found that hexamethonium is the ganglionic blocking agent of choice here and that it should be given parenterally The reason for our preference for hexamethonium is the ease of administration (it can be given intramuscularly or intravenously) and the fact that it has an intermediate length of action The length of action of mecamylamine is prolonged and thus may be a problem should an excessive response be obtained Arfonad must be given by continuous intravenous infusion and the length of action is very short Under some circumstances this may be preferable and in fact the hypotensive effect of Arfonad seems to be greater than the response to the other ganglionic blocking agents Therefore in patients who do not respond to hexamethonium Arfonad should be given a trial

When hexamethonium is given intravenously we usually place 10 mg in a 10 cc syringe of 5 per cent glucose This is then injected slowly over a 10 to 15 minute period At any time that a definite reduction in blood pressure is obtained the administration of the blocking agents should be temporarily discontinued awaiting the maximum response to the drug that has already been given After this has been observed the therapist can then give the additional amount of the drug that is indicated (depending on blood pressure response) or may switch to the intramuscular route Depending on the response the subsequent doses of the drug are increased in 10 to 15 mg increments until an adequate reduction in blood pressure is obtained At any time that the blood pressure is reduced adequately the drug is discontinued until a significant rise in blood pressure occurs toward the pretreatment value indicating that further antihypertensive therapy is required

Concerning the renal effects of ganglionic blocking agents there is a temporary reduction in glomerular filtration rate and renal blood flow associated with depression in urine volume and sodium excretion as indicated by Ford [1] However with long term therapy readjustment occurs in patients who do not have serious renal damage and depression of renal function is not significant Table 5 compares the renal hemodynamic response to three ganglionic blocking agents It is obvious that there are no significant differences among the various compounds With prolonged administration the depression in glomerular filtration rate in the supine position is not signifi

cant unless the blood pressure is reduced excessively However when changing from the supine to the upright position there is a definite reduction in glomerular filtration rate associated with the sudden decrease in mean blood pressure (Table 5) when standing A similar reduction in glomerular filtration rate occurs in patients who do not receive ganglionic blocking agents when changing from the supine to the upright position However in the unblocked patient the blood pressure responses are not as marked (Table 5)

TABLE 5 COMPARISON OF THE RENAL HEMODYNAMIC RESPONSE TO MECAMYLAMINE HEXAMETHONIUM AND PENTOLINIUM IN PATIENTS RECEIVING THE DRUGS FOR PROLONGED PERIODS OF TIME

	NUMBER OF PATIENTS	CONTROL	DRUG	PER CENT OF CONTROL	P VALUE	TILT	PER CENT† DRUG SUPINE	P VALUE
			Mean Blood Pressure (mm Hg)					
Mecamylamine	11	156	130	83	001	108	83	001
Hexamethonium	7	159	131	84	001	104	78	001
Pentolinium	11	146	118	81	001			
Untreated	20	141				126		001
			Glomerular Filtration Rate (ml /min)					
Mecamylamine	11	81	75	93	2	54	72	01
Hexamethonium	7	73	71	97	1	56	79	02
Pentolinium	11	83	80	96	1			
Untreated	20	80				51		01
			Renal Blood Flow (ml /min)					
Mecamylamine	11	810	731	90	2	518	71	01
Hexamethonium	7	801	815	102	1	501	61	01
Pentolinium	11	866	963	111	1			

Mean Blood Pressure—Diastolic pressure plus one third of pulse pressure
Control—Control recumbent
Drug—Drug recumbent
Per Cent Control = Drug/Control × 100
P Value—Comparison of Control with Drug A P value of less than 05 is significant
† Per Cent = Tilt/Drug × 100
P Value—Comparison of Drug with Tilt

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The Rationality or Irrationality of Ganglion Blocking Agents in Hypertension

W D M PATON

Royal College of Surgeons England

INTRODUCTION

I have regarded this title a most provocative one as an invitation to the higher speculation and will simply set out my own thoughts as clearly as I have been able to formulate them in the hope that they may at least bring out into the open some of the unspoken assumptions in the use of ganglion block

A laboratory worker is of course hampered straight away by the realization that there seems no agreement on a rational etiology of hypertension Obviously unless one knows the cause of a disease it is difficult to discuss its treatment in any but empirical terms But for hypertension there seems to be no specific account of pathogenesis so convincing as to command general assent In a sense there are too many possible explanations and many shrewd clinicians noticeably refrain from chancing their arm as to which explanation it is that they really back The main concepts are perhaps the following (1) Hypertension is neurogenic in origin in the sense that in the hypertensive patient the prime mover is an abnormal activity of his autonomic nervous system leading to a sustained sympathetic tone and rise in blood pressure (2) The increased peripheral resistance is due not to nervous influences but to a circulating vasoconstrictor substance Most plausibly this is a factor originating from changes in the kidney less plausibly a sympathetic amine (3) The abnormality is in neither of these directions but in the blood vessels themselves so that they respond to ordinary influences whether nervous or hormonal by an exaggerated contraction or the responsiveness of their muscle is not specially modified but their structure is such that their lumens at normal muscle tone are smaller than usual (4) It seems to be implied in some treatments that the fundamental defect is connected primarily with the adrenal cortex and that the ensuing changes in electrolyte and fluid distribution result in hypertension There are of course other suggestions But these four seem pretty representative in placing the lesion respectively in the nervous system in circulating hormones in the vessels themselves or in the control of the volume of blood perfusing them I have taken it as my duty being interested in ganglion block to select the first as being *the* cause of hypertension I propose therefore to argue this case and further that so far as the other explanations are true it is because they are sequels to hypertension of nervous origin The material of the argument of course is those patients who begin symptomless and with no detectable pathology save the sign of a raised blood pressure and of

whom a small proportion proceed to the characteristic and distressing picture termed malignant hypertension

ARGUMENTS FOR THE NEUROGENIC HYPOTHESIS

I can see four arguments in favor of hypertension being primarily due to an overactivity of the autonomic nervous system They are of course also justifications for the use of ganglion block

1 The first which can be called briefly the *geographical argument* may be put thus In the early days of hexamethonium one objection was sometimes raised to its use that the raised blood pressure in hypertension is a valuable protective response preserving a satisfactory blood flow to the organs in which a narrowing of arterioles had occurred This implied that to lower the blood pressure might deprive vital organs of their necessary blood flow It seems to me quite correct to predict that lowering the blood pressure *per se* could well be harmful—except under one circumstance this is if the reduction in blood pressure was achieved by means which dilated those very vessels which were constricted by the hypertensive process Clearly it would be no use for instance, to vasodilate muscle blood vessels selectively if the vasoconstrictive process also affected viscera skin heart brain suprarenals and so on Equally one would not expect successful therapy from a general vasodilatation if the pathologic vasoconstriction was spatially limited But if the geography so to speak of the vasodilatation on which the blood pressure fall depended was the same as the geography of the vasoconstriction on which the hypertension depended blood flows would be little altered and the benefit of a smaller hydrostatic pressure in the arterioles would be gained One could infer then from the fact that ganglion blocking agents are so effective that the nature of the vasoconstrictive process which gives rise to hypertension has the same distribution as the vasodilation produced by ganglion block Since the distribution of ganglion block is necessarily that of the autonomic nervous system one then has an argument that the distribution of the vasoconstrictor process in hypertension is also that of the sympathetic autonomic nervous system

It could be objected however that almost *any* method of lowering the blood pressure is also effective in hypertension But it is interesting how many of the effective attacks are like ganglion block through the autonomic Sympathectomy Veratrum alkaloids (whose important action seems to be *the relief of sympathetic tone) central depressants reserpine (attacking* centrally and also more specifically the adrenergic nerves) all have this in common It is perhaps significant that nitrites have not been very successful nor lowering the blood pressure by arteriovenous fistula A more searching objection would be to say that paralysis of the sympathetic outflow will have such a diffuse action that *any* diffuse vasoconstriction should be countered by it Nevertheless the fact that our modern treatment of hypertension focuses anatomically so much on the autonomic justifies a special interest in autonomic causes for the disease

2 The second argument for a nervous cause starts with the premise that if the blood pressure rises from any of the other causes one would anticipate that the neurogenic tone in the patient would be reduced by the normal operation of the buffer nerves The scope of action of an autonomic blocking agent should be much smaller than in the normal individual But of course

the practical result is the reverse a normal individual supine shows usually a trivial fall in blood pressure whereas a supine hypertensive exhibits a substantial one Therefore neurogenic tone is increased not decreased in hypertension and the other causes do not operate A good deal depends here on the validity of the premise It is easily verified in one way thus if one infuses a peripheral vasoconstrictor into an animal so as to raise the blood pressure ganglion blocking agents now have rather a small depressor action On the other hand if one raises the blood pressure by some method involving an increase in autonomic tone such as asphyxia or by establishing a rather light plane of anesthesia then ganglion blocking agents can be extraordinarily effective

However it may be objected that this type of test is too acute Green McCubbin and Page produced evidence that if a *sustained* humoral hypertension was achieved in dogs then the buffer nerve afferent discharge initially very vigorous steadily fell away as though this sensory area became accommodated to its new situation From this experiment one would suppose that the autonomic efferent discharge in the hypertensive could return to a state comparable to that seen in a normal individual even if the hypertension was humoral However we are still left with the difficulty of explaining with this sort of model why ganglion blocking agents work *better* in the hypertensive than in the normal Even if there is some degree of autonomic activity one could not predict that when it is removed in the presence of a strong humoral vasoconstriction any substantial fall of blood pressure would necessarily occur any more than one would expect that if two strong men are holding up a weight and one lets go the other one will necessarily let it fall I would like to suggest that in fact the natural history of hypertension provides us with a model experiment Some cases begin fully sensitive to autonomic block and then develop a fixed high blood pressure progressively resistant to block and accompanied by such signs of arteriolar damage that one is willing to suppose that renal humoral factors have taken control The fixity of the blood pressure at this stage underlines the significance of its lability at an earlier phase

A second objection can also be raised that the large fall of blood pressure produced by ganglion block in many hypertensives is due not to an increased autonomic nervous discharge from the C N S but to an increased reaction by the blood vessels to a normal discharge To support this notion some workers (though not all) report an increased response to vasoconstrictor drugs in hypertensives compared to normal Perhaps one should wait until this is established But two comments can be made First it does not lessen the importance of neurogenic tone since it implies that given a small backing of some hormonal vasoconstrictor neurogenic influences become far more important than they might be believed to be from tests on normal individuals As neurogenicity is expelled at one door it comes back with renewed force at another! Second if a given quantum of nervous activity yields a bigger effector response than normally one would expect homeostatic mechanisms to check this response by reducing the intensity of the nervous discharge so keeping blood pressure near its proper level The argument of exaggerated vessel reactivity may explain some of the facts but by itself cannot explain the most important one the hypertension itself

3 The third argument bases itself on the relative commonness of hypertension and on the evidence provided by Pickering and his colleagues and

by others that blood pressure is a unimodally distributed quantity that in other words hypertensives are the right hand tail of a distribution curve This means that for its pathogenesis we must look for a cause which is both common and an extension of normal processes What common normal hypertensions are there? As far as I know those mediated by the autonomic in so called "stressful" situations are the only examples one can quote If our everyday life is made up of fluctuations in blood pressure in response to circumstance it seems perfectly reasonable to suppose that sometimes these fluctuations may become more prolonged and more persistent than usual To look further for a *primary* cause of hypertension seems rather like trying to explain the popularity of pin up girls not by the attractiveness of the girls portrayed but on a theory say that young men like hammering tacks into walls!

4 The fourth argument one can advance is that the whole picture of hypertension is interpretable by taking a neurogenic starting point By this I mean that if one postulates an initial autonomic activity one can then readily suppose that in due course the blood vessels through their exposure to a higher hydrostatic pressure through the years will change in their structure and diameter that this autonomic activity could be associated with an excitation of the adrenal cortex perhaps mediated via adrenalin secretion and the anterior pituitary leading to those evidences of sodium retention and aldosteronism which have been put forward and that in the course of time as arteriolar damage becomes worse renal damage may follow in turn to produce a supplementing and finally dominant renal hypertension This is a picture which speculative though it is I believe many people take as a working model Its attraction seems to be simply that it provides a sequential analysis of hypertension which does not seem to flow so plausibly from the other approaches I do not know for instance of any satisfactory physiologic evidence that an adrenocortical overactivity could commonly give rise to a physiologic state which could be interpreted as autonomic overactivity although as just mentioned one can envisage a state in which autonomic overactivity could give rise to adrenocortical activity

One can therefore propose that the prime cause of hypertension is a sympathetic overactivity and that the features of its later development have been elicited by this initial neurogenic excitation

SOME OBJECTIONS

There are however still some objections to meet The first bears almost directly on pharmacology If you give a ganglion blocking agent to a hypertensive it seems that the blood pressure only rarely falls to the same level observed for a normotensive This provides the basis for the allotment of the excess of blood pressure over the normal into a neurogenic and non neurogenic fraction I am not sure however that this necessarily holds because of the difficulty in producing complete ganglion block One must remember for instance that it is usually impossible to produce in an animal with any dose of ganglion blocking agent a blood pressure as low as that achieved by anesthesia or destruction of the spinal cord My own guess which I have argued elsewhere is that the accessory ganglia those cells located not in the pre and paravertebral ganglion chains but in the rami

or in spinal nerves are as resistant to drugs as they are elusive to the surgeon s scalpel and that this resistance is a result of their still being cloaked by an extension into peripheral nerve of the blood brain barrier In apportioning the division between neurogenic and non neurogenic it is not enough simply to record the lowest blood pressure obtained with a large dose of blocking agent it is also necessary to prove that *all* vasomotor responses have been obliterated If they have not been there may well be an additional neuro genic fraction of pressure still present Clearly, if the pressure floor rises as observations continue in a deteriorating patient one could attribute the increment to non neurogenic factors But the initial apportionment offers considerable difficulties and a relatively high floor in a first test cannot be directly attributed to say humoral influences

A second objection arises from the known association of rising blood pressure with increasing age It is difficult even for a fervent speculator to assume that autonomic activity will increase not only up to the prime of life but beyond it even to the age of the lean and slippered pantaloon especially when the structural changes in the arteries which age brings are so obvious It could be argued however that the rise with age represents not a primary degeneration of the blood vessels but the result of a lifetime of autonomic activity that every autonomic adventure leaves its debris on the sands of cardiovascular time One can note too that it is estimated that age constitutes only about one fifth of the total sources of variation which determine blood pressure Nevertheless one should probably admit that with advancing age the rising normal blood pressure provides a steadily higher base line from which other pressor processes will start The other aspect of this study demonstrating a multifactorial inheritance of blood pressure level is not of course indicative of any particular pathogenesis It was around 50 years ago that Francis Galton in his fascinating book *Hereditary Genius* showed that qualities like scientific military or political ability even the stringent demands of ecclesiastical distinction and piety were inherited If these complicated faculties can be passed on by the genes variations in the humbler autonomic function should not be beyond their capacity

The last objection to the neurogenic hypothesis is perhaps that the evidence for it is so largely circumstantial To a large extent it rests on so to speak the method of subtraction—that is by comparing the physiologic state of a subject before and after some measure of autonomic attack and attributing the difference to autonomic factors But we have seen some of the difficulties of the method particularly on the quantitative side Can more direct evidence be obtained? The prospect does not look very hopeful For one cannot record action potentials directly in human autonomic nerve pathways Nor does it seem that we can identify sympathetic activity by nor adrenalin release The noradrenalin excretion of hypertensives (apart from pheochrome tumors) is hardly different from normal This might be taken as evidence against a neurogenic hypothesis But we know that of an infused quantity of noradrenalin only around 3 per cent appears in the urine the fraction that would be excreted of that released at sympathetic nerve endings could only be minute when it has been exposed to destruction at the site of release and to dispersion throughout the body On the back ground of normal catechol amine output any output from this cause could well be undetectable

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The Use of Hydralazine Combined with Ganglion Blocking Agents in Hypertension

H M PERRY, JR
Washington University School of Medicine St Louis

My discussion of the combined use of hydralazine and ganglion blocking agents to control elevated diastolic pressure is divided into two parts The first contains an outline of the particular regimen which we have found to be most effective The second briefly considers a pair of observations that we have made on patients so treated One observation involves mortality rates in patients with severe hypertension and the other involves the suggestively diminishing drug requirement in less severely hypertensive patients

THERAPEUTIC REGIMEN

The ultimate objective in treating the most severe types of hypertension is to prolong life With less serious hypertension the ultimate objective is to lessen those changes associated with elevated diastolic pressure In either situation the immediate objective of therapy is continuous control of diastolic pressure at normal or nearly normal levels Such control can ordinarily be accomplished by currently available antihypertensive drugs the most potent of which is the ganglion blocking agent Since the first clinically practical ganglion blocking agent hexamethonium was not entirely satisfactory it was natural to administer hydralazine (Apresoline) simultaneously Because no untreated patient seemed completely resistant to this combination of drugs we used it exclusively for several years in an attempt to evaluate its efficacy At present other antihypertensive drugs such as tranquilizing and diuretic agents are being widely used alone and in combination but we have no comparably detailed data regarding them

It should be emphasized that this regimen like most regimens which lower markedly elevated diastolic pressure is often initially unpleasant Many physicians who have prescribed it have been unable to convince themselves or their patients that diastolic normotension warranted the associated side effects For our original four patients with malignant stages of hypertension and its prognosis of only a few months no inconvenience seemed excessive It was unexpected and very encouraging to find that the side effects of treatment tended to disappear after a period of adequately controlled diastolic pressure

The general plan of therapy is to administer a ganglion blocking agent in gradually increasing doses until the average diastolic pressure approaches the desired level Hydralazine is then added in hope of obviating both the wide fluctuations in pressure and the tolerance which characterize the use of ganglion blocking agents alone Since the required amount of ganglion

blocking agent often varies considerably and in a nonpredictable way some method of relating each dose of drug to the level of blood pressure seems advisable In nonazotemic patients most of the absorbed blocking agent is excreted in the urine within a few hours hence frequent dosage is necessary to maintain relatively constant circulating concentrations The more prolonged action of hydralazine does not prevent the administration of both drugs at the same time in order to avoid separate dosage schedules

At present the best clinically available ganglion blocking agents are pentolinium (Ansolysen) chlorisondamine (Ecolid) and mecamylamine (Inversine) Comparable oral starting doses are 20 12 5 and 2 5 mg respectively Pentolinium and chlorisondamine are very similar Mecamylamine is somewhat different it has the advantage of being more completely absorbed from the gastrointestinal tract but the disadvantage of having produced neurologic manifestations in azotemic patients Although the three can be used almost interchangeably for the sake of simplicity only pentolinium will be considered Therapy is begun by giving small doses of ganglion blocking agent such as 20 mg of pentolinium every four hours day and night unless the systolic pressure is below some predetermined level such as 140 mm Hg After 24 hours each dose is increased by 20 mg to a total of 40 mg and at daily intervals each dose is increased by similar increments until the mean systolic pressure approaches a satisfactory range such as from 125 to 140 mm Hg In an attempt to maintain the pressure within or near the satisfactory range full doses of ganglion blocking agents are prescribed for pressures above the upper limit of the range and half doses are prescribed for pressures within the range No ganglion blocking agent is given for pressures below the lower limit of the range

When the mean diastolic pressure approaches the desired level 25 mg of oral hydralazine is administered every four hours At daily intervals each dose of hydralazine is increased by 25 mg until the intake of hydralazine approximates that of pentolinium Roughly equal amounts of the two drugs seem to give optimum results but final regulation of blood pressure is accomplished by increasing the dose of ganglion blocking agent if the average pressure is too high or by increasing the dose of hydralazine if fluctuations in pressure are too great

Although side effects eventually diminish initially it may be necessary to ameliorate them insofar as possible The side effects of parasympatholysis are the only ones amenable to countermeasures Constipation and urinary retention can be dangerous amblyopia dry mouth cold intolerance nasal congestion and impotence are annoying With quaternary ammonium blocking agents like pentolinium and chlorisondamine constipation leads to an accumulation of the drug in the gastrointestinal tract and a resultant increase in the fraction absorbed High fluid and fruit intake laxatives enemata and in rare instances parasympathomimetic drugs such as 2 5 to 10 or even 20 mg of oral Urecholine may be temporarily required with every dose of ganglion blocking agent Persistent constipation is often improved with reserpine which however usually causes some gain in weight and less frequently leads to severe depression or peptic ulceration If urinary retention is uncorrected it may produce infection and thereby further decrease renal function unfortunately there is no adequate substitute for surgery when prostatic hypertrophy is present Fortunately few severe side effects of hydralazine manifest themselves in patients pretreated with ganglion blocking

agents We have experienced no difficulty in sending patients home with a sphygmomanometer and instructions for regulating their pressures at approximately normotensive levels with variable doses of ganglion blocking agent and invariant doses of hydralazine This combined regimen has been discussed in more detail elsewhere [1]

FOUR YEAR SURVIVAL AMONG TREATED MALIGNANT HYPERTENSIVE PATIENTS

The combination of ganglionic blockade and hydralazine has been used for only relatively short periods of time hence its effect on life expectancy can be evaluated only in seriously ill patients with significant and predicta

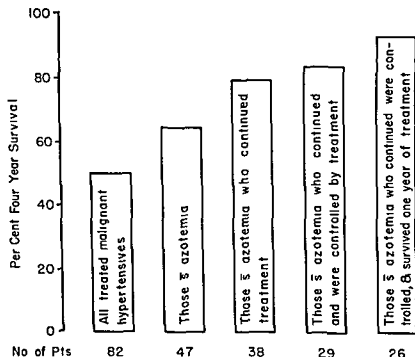


Fig 1 Mortality rates for various categories of malignant hypertensive patients

ble mortality rates during the available observation period We began such treatment on 82 patients with malignant stages of hypertension more than four years ago These patients represented a consecutive series of previously untreated nonuremic adult patients with no exclusions because of the severity of hypertension or discontinuation of therapy All of these patients had papilledema as well as hemorrhagic and/or exudative retinitis all had mean supine diastolic pressures greater than 120 mm Hg at hospital rest all had proteinuria and diminished excretion of phenol red Thirty five of the 82 were azotemic Every patient was followed for four years but nothing that happened to him thereafter was considered

Forty one or exactly half of the 82 patients survived four years of therapy but the prognosis was much better for the one out of three who was

nonazotemic and cooperative who succeeded in controlling his blood pressure and who survived the first year of therapy Of the 47 patients who were not azotemic 30 or 64 per cent survived four years All nine patients who discontinued taking one or both of their drugs died within four years of beginning therapy so that of the 38 nonazotemic patients who continued therapy 30 or 79 per cent survived four years Of the 29 nonazotemic cooperative patients whose average supine diastolic pressures in the hospital had been controlled at levels below 100 mm Hg 24 or 83 per cent survived four years The first 12 months of therapy were the most perilous three of the 29 nonazotemic cooperative and adequately controlled patients dying within that period and only two dying during the next 36 months Therefore of the 26 nonazotemic cooperative and adequately controlled patients who survived a year of therapy 24 or 92 per cent survived an additional three years of therapy Figure 1 summarizes these data which have been presented in detail elsewhere [2]

CHANGING DRUG REQUIREMENT NEEDED TO MAINTAIN CONTROL OF BLOOD PRESSURE

Among patients with less severe hypertension the intake of antihypertensive drugs required to maintain the diastolic pressure at relatively normal levels has been tabulated The basis for the subsequent comments are 114 patients who were treated with ganglionic blockade and hydralazine but no other antihypertensive agents and who took their blood pressures at home in the sitting position four or five times a day for from one to three years These patients were divided into three arbitrary groups solely on the basis of their average pretreatment supine diastolic pressures in the hospital Forty patients belonged to the *mild* group with diastolic pressures from 100 through 114 mm Hg 41 to the *moderate* group with pressures from 115 through 129 mm Hg and 33 to the *severe* group with pressures from 130 through 160 mm Hg Each of these three groups was subdivided into two arbitrary subgroups solely on the basis of their average post treatment sitting diastolic pressures at home Thirty five patients with diastolic pressures of 100 mm Hg or more one year after leaving the hospital were placed in the *uncontrolled* subgroups the other 79 patients were placed in the *controlled* subgroups Of the 114 patients whose records were available for one year 78 were followed for two years and 37 for three years The daily intake of ganglion blocking agent and hydralazine one month after hospital discharge was compared with the intake of these drugs one year and when possible two and three years later

One month after hospital discharge the 79 *controlled* patients were ingesting an average of 2 02 gm of hexamethonium and 0 50 gm of hydralazine per day After one year at home they were taking about three fourths of that original dose of hexamethonium and nine tenths of that original dose of hydralazine After three years of treatment the intake of both hexamethonium and hydralazine had fallen to about half of the original dose During three years of therapy their diastolic pressures had decreased slightly but not significantly from the mean values one month after hospital discharge In contrast the 35 *uncontrolled* patients had not diminished their intake of either antihypertensive agent after one year of treatment and after three years they were still taking four fifths of their original doses of both agents

During three years of therapy their diastolic pressures had increased slightly but not significantly from the mean values one month after hospital discharge The table summarizes these data which have been presented in detail elsewhere[3]

CONCLUSION

The combination of ganglionic blockade and hydralazine like other regimens which lower diastolic pressure is capable of prolonging the life of many patients with severe hypertension Perhaps even more encouraging is the suggestion that patients with less severe hypertension who control their

TABLE 1 DRUG DOSAGE FOR 114 VARIOUSLY SEVERE HYPERTENSIVE PATIENTS (AS PERCENTAGE OF DOSE REQUIRED ONE MONTH AFTER HOSPITAL DISCHARGE)

Pre Rx Diastolic	Post-Rx Diastolic	One Year % Hex	One Year % Hyd	Two Years % Hex	Two Years % Hyd	Three Years % Hex	Three Years % Hyd
100-114	<100	64	83	37	58	42	58
115-129	<100	81	89	69	68	31	41
≥130	<100	80	99	76	107	60	71
Total	<100	74	89	55	71	42	55
100-114	≥100	91	90	88	96	84	77
115-129	≥100	87	99	106	85	96	75
≥130	≥100	110	102	93	77	69	81
Total	≥100	97	99	97	86	84	77

diastolic pressures at or near normal levels require gradually diminishing amounts of antihypertensive agents to maintain this degree of control

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Clinical Use of Ganglion Blocking Agents in Essential Hypertension

GARFIELD G DUNCAN

University of Pennsylvania

Ganglion blocking is a highly individualized form of therapy for essential hypertension the effectiveness of ganglion blocking drugs being modified by selection of the patients for this form of therapy selection of the agent most likely to give optimum benefit dosage distribution side effects and their prevention choice of other drugs which supplement this form of therapy continuity of treatment and training of the patient

SELECTION OF THE PATIENT

Potent blocking drugs are contraindicated for those patients whose hypertension can be controlled by more conservative means Detection of the degree of lability of the diastolic pressure under the influence of sedation produced by Sodium Amytal given in three doses of 0 2 gm each at one hour intervals is a valuable aid in predicting whether or not a ganglion blocking agent will be necessary A fourth dose of Sodium Amytal is given if necessary to produce sleep during the test We use this test freely doing it usually on the day the patient is admitted to the hospital If during the

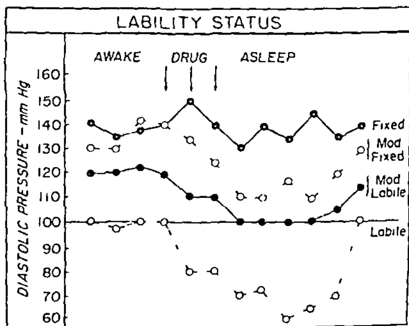


Fig 1 The responses of the diastolic pressures to 0 2 gm of Sodium Amytal given orally at one hour intervals for three doses indicate four degrees of lability labile moderately labile moderately fixed and fixed

test the diastolic pressure falls to or below the arbitrary level of 100 mm Hg its lability is such as to contraindicate ganglion blocking agents Patients whose pressures behave in this manner are especially prone to "blacking out" sensations should these drugs be employed Should the diastolic pressure decrease perceptibly but not to 100 mm Hg it is considered safe but not always necessary over long term treatment to use a ganglion blocking agent whereas if the elevated diastolic pressure is fixed or altered but little as indicated by the top graph in Figure 1 this therapy is embarked upon at once A more tedious more expensive and needless method of getting the same information is to observe the hospitalized patient for two or three weeks under conservative drug therapy If other means have indicated the

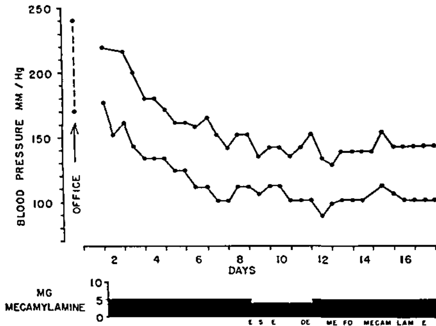


Fig 2 The effect of mecamylamine therapy plus sodium depletion (not indicated in figure) in the case of a fixed diastolic hypertension is indicated Continued improvement without altering the dosage is attributed to the enhanced effect which sodium depletion exerts on mecamylamine therapy

diastolic pressure to be labile or moderately so the Sodium Amytal test would not be considered necessary On the basis of years of experience[1] with the Sodium Amytal test as an aid in establishing the degree of lability of the diastolic pressure it can be said that patients who "black out" with ganglion blocking agents have the type of pressure that does not require this therapy Patients with fixed diastolic pressure response may become giddy from over dosage but none of my patients in this group has ever blacked out

SELECTION OF THE GANGLION BLOCKING AGENT

Though none of these drugs is ideal they may be lifesaving nonetheless The drug most likely to yield optimum clinical results is one which is com

pletely absorbed quickly and uniformly which exerts a prompt as well as prolonged hypotensive effect and which when combined with other hypotensive drugs causes a minimum of unfavorable side effects Of the ganglion blocking agents mecamylamine is superior in these respects to hexamethonium pentolinium tartrate and chlorisondamine chloride (Ecolid)

The development of drug tolerance as treatment proceeds is least marked with mecamylamine It is with this drug that improved control of the hyper tension without adding to the dosage often occurs and reduced amounts may suffice after a few weeks of therapy and after the patient resumes nor mal activities (Fig 2)

Though we have found mecamylamine preferable to other blocking

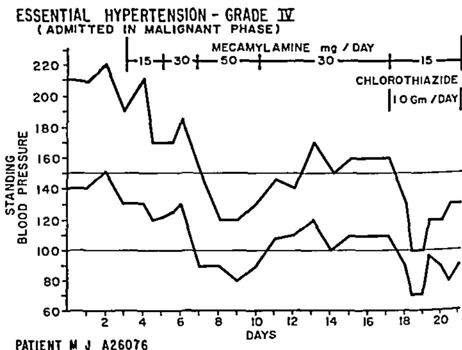


Fig 3 Satisfactory control of malignant hypertension with 50 mg of mecamylamine daily in the early phase of therapy is indicated A reduction to 30 mg a day resulted in poorer control but when only 15 mg a day was given in conjunction with 1 gm of chlorothiazide daily excellent control ensued

agents this does not mean that good results are not obtainable with other members of this group Indeed some patients whose hypertension was well controlled have continued with pentolinium tartrate In general however the small percentage of hexamethonium pentolinium (Ansolysen) and chlorisondamine (Ecolid) absorbed from the gastrointestinal tract the in creased absorption if constipation prevails and the reduced absorption caused by diarrhea make mecamylamine which is quickly and completely absorbed the ganglion blocking agent of choice

To secure optimum results with minimal side effects the initial doses of mecamylamine should be small—1 25 mg three times daily If each dose is increased by no more than 1 25 mg at two- or three day intervals a gradual

adaptation of varying degrees to the drug is permitted In this manner unfavorable side effects are kept at a minimum. Blood pressure readings taken four times daily during the early titration are guides to the dosage for the individual patient The aim is to secure systolic pressures between 110 and 160 mm.Hg with the patient in the standing position This degree of perfection as recommended by Smirk is desirable if reasonably innocent pressures are to prevail when the patient is in the sitting or lying position One patient may require 2 5 mg or less of mecamylamine at approximately eight hour intervals whereas another may need several to many times this amount An occasional patient does better with four doses in the twenty four hours

Reserpine and chlorothiazide are invariably used in connection with

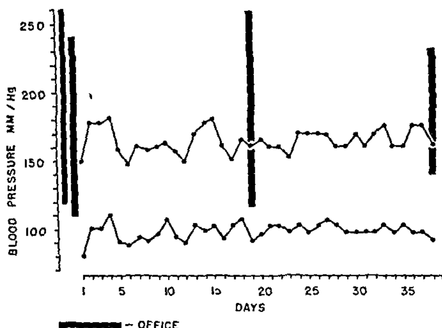


Fig 4 Satisfactory home blood pressure readings in the case of a relatively fixed diastolic hypertension are compared with unsatisfactory pressures obtained in physician's office

mecamylamine therapy except in the presence of azotemia when the reduction of blood pressure is brought about cautiously and when sodium depletion has occurred hence chlorothiazide therapy is contraindicated Other tranquilizing agents are used to replace reserpine if this drug causes the patient to be depressed Less mecamylamine is needed side effects are minimal and more uniform control of the blood pressure is achieved when this combined therapy is employed as indicated in Figure 3

Intensive anticonstipation measures are part of the initial routine therapy with mecamylamine but with small initial doses of this drug increased by small increments constipation usually ceases to be more than a minor

problem after a few weeks of therapy Pilocarpine nitrate in doses of 5 mg two or three times daily will reduce the effects of parasympathetic blockade It tends to reduce the dryness of the mouth disturbances in vision and the degree of constipation and usually overcomes the atony of the bladder occasionally encountered in the elderly male patient Like the intensive anti constipation measures pilocarpine is usually needed only in the early phases of treatment

Emotional disturbances may obscure for short periods the effects of ganglion blocking agents Blood pressure readings in a physician s office may reflect this effect as indicated in Figure 4 When practicable home blood pressure readings are of value in adjusting the dosage When these are impracticable the respective doses are adjusted until they are just short of causing slight giddiness when the patient rises from lying or sitting to the upright posture Adjustment of the dosage on the basis of high blood pres sure readings obtained in the office is likely to intensify unfavorable side effects and to discourage the patient

More effective control of the hypertension in the most severe cases may be secured by adding hydralazine 25 to 50 mg three or four times daily to the basic therapy mentioned above We have avoided doses of this drug that total more than 200 mg daily This amount or less when used in combined therapies may have a salutary effect Whether or not this effect is sustained over long periods is open to question

CONTINUITY OF GANGLION BLOCKING THERAPY

Withdrawal of a ganglion blocking drug is followed by a return of un controlled hypertension as indicated in Figure 5 This result is more gradual following the withdrawal of mecamylamine than when other ganglion block ing agents in current use are discontinued In fact in the case of the latter the hypertension has been observed within twelve hours without the drug to exceed levels which preceded ganglion blocking therapy Patients must be aware of this possibility Despite adequate instruction some patients be cause of their improved feeling of well being stop all therapy Vascular accidents and myocardial decompensation have been observed to ensue It is in such cases of unreliability that sympathectomies are of value Sympa thectomy may be a means of saving a patient from the folly of his own actions By sensitizing the patient to more conservative drug therapy an adequate sympathectomy in all but rare cases permits the discontinuance of the ganglion blocking agent

On the other hand when there is no break in the continuity of treatment regression of the unfavorable effects of hypertension is the rule It is well known however that in some patients and especially in those in whom evidences of atherosclerosis predominate vascular disease may continue its unfavorable course Nevertheless in most cases the apparent effects of hy pertension tend to recede with continued control of the hypertension

Patients admitted in hypertensive crisis whether it be acute myocardial failure secondary to the hypertension intracranial hemorrhage or encepha lopathy are treated with other measures notably intravenously administered protoveratrine or a less uniformly effective agent reserpine given paren terally With control of the crisis ganglion blocking therapy is begun and is adjusted gradually to the desired amounts Attempts to control the crisis by

ganglion blockade invites the risk of a paralytic ileus or disturbed bladder function which is needlessly confusing in a patient who may be unconscious

INSTRUCTION OF THE PATIENT

Detailed instruction regarding the diet and notably the degree of sodium restriction is important The patient is warned of the possibility of "blacking out" although this is not a problem if patients are properly selected for ganglion blocking therapy Most important is that the patient must know that he has a disorder which though not curable is controllable and that

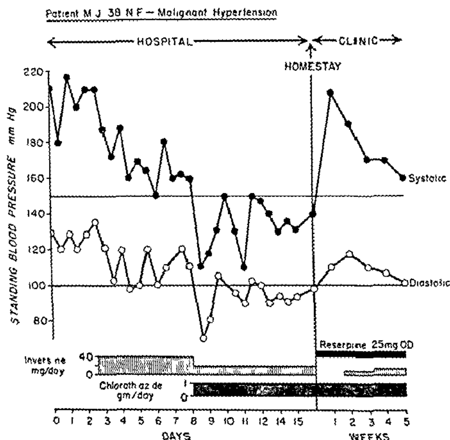


Fig 5 Mecamylamine therapy is supplemented with advantage by chlorothiazide therapy Because of well being drugs were discontinued by patient Hypertension returned but relatively good control was resumed by the basic therapy reserpine chlorothiazide and mecamylamine

treatment—not even a single dose of the drug—should not be interrupted It is well to warn the patient that if he has regained a comfortable state of health it is because of good control of his disorder and not because a cure has been effected hence it is an indication for continued therapy rather than reduction or discontinuance of measures which are satisfactorily effective

When practicable instructions in the technique of taking and recording the blood pressure are given to a relative or friend Two home readings two

days per week usually suffice The advantages of home blood pressure readings have been emphasized by Smirk and Freis[3]

CONCLUSIONS

It may be emphasized (1) It is for the patient with a fixed or a relatively fixed diastolic hypertension that the ganglion blocking therapy should be employed this represents a minority approximately 12 to 15 per cent of the patients with hypertension (2) The lability of lesser degrees of hypertension contraindicates the use of ganglion blocking agents (3) The revival of the Sodium Amytal test has made it possible to determine the lability of the diastolic pressure within a matter of hours (4) The patient who "blacks out from ganglion blocking therapy can be effectively treated with more conservative measures (5) Patients requiring ganglion blocking therapy should have treatment individually standardized in a hospital when practicable (6) Mecamylamine at the moment is the ganglion blocking agent of choice (7) Side effects are most troublesome in the early few weeks of therapy and become ameliorated with prolonged control of the hypertension especially when the basic treatment comprises restriction of sodium to 1 gm reserpine or other tranquilizer and chlorothiazide in addition to mecamylamine Patients should be prepared for side effects in the early phase of treatment and should be reassured concerning later favorable progress otherwise they may insist on abandoning the treatment (8) Sodium depletion by reduced sodium intake and chlorothiazide therapy permits a reduction in the dosage of mecamylamine by one half or more Finally (9) barring cases of renal failure relatively good control of the hypertension is achievable in nearly all cases of hypertension

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Retinal Vascular Changes in Hypertension

ALBERT A BRUST
University of Cincinnati

Of the various target organs which may be affected by hypertension none is so readily available for direct study as the ocular fundus Clinical appraisal of the severity of hypertensive disease has come to be based in part on the changes observed in the retinal blood vessels and allied structures Thus the appearance of hemorrhage exudate or papilledema in the eye

grounds of a hypertensive patient is believed by many to suggest the advent of an accelerated phase of the disease Similarly in follow up evaluation of hypertensive *patients treated with depressor drugs* diets and surgical procedures considerable significance has been assigned to the clearing of retinopathy which was previously present

It is the purpose of this paper to report certain observations of the human retina during a five year study of the natural history variability and reversibility of retinal vascular lesions Serial photographs in the same patients were correlated with the clinical course of the disease in an effort to clarify both the diagnostic and prognostic importance of the retinal changes in accelerated hypertension Although the photographs themselves cannot be reproduced here representative examples have been published elsewhere *

ANATOMIC CONSIDERATIONS

When the *central retinal artery* enters the fundus through the optic nerve head it promptly gives off a major superior and inferior branch each of which divides into temporal and nasal branches As the retinal arteries successively subdivide into smaller radicles they give off their branches at approximately right angles After the second branchings the arteries lose their muscular coats and properly may be termed arterioles Eventually they become *capillaries* and *extend more deeply into the retina Corresponding in* general distribution to the arteries are the broader darker colored veins whose smaller branches join to form larger channels which finally penetrate the optic disk and leave the fundus as the *central retinal vein* The *macula lutea* located exactly at the posterior pole of the eye subserves central vision is devoid of visible blood vessels and appears somewhat darker in color than the surrounding fundus The major fundal vessels course among the unmyelinated fibers of the *nerve fiber layer (stratum opticum)* of the retina The nerve fibers running parallel with the surface of the retina traverse the fundus to converge at the optic disk and determine in large measure the shape position and characteristic configuration of certain of the hemorrhagic and exudative retinopathies In general the fibers radiate toward the disk like the spokes of a wheel converging at the hub Fibers emanating from the macular region however are grouped into a roughly elliptical bundle with the disk and macula describing the major axis This anatomic arrangement is likewise important as it figures prominently in defining the pattern of certain retinal lesions and in determining the course of migration of edema residues away from the disk

When blood is extravasated into the nerve fiber layer of the retina it is free to extend longitudinally between the fiber bundles which are arranged in a plane parallel to the retinal surface The long axis of such hemorrhage therefore follows the course of the nerve fibers themselves and appropriate descriptive terms such as *linear elongated streak* and *flame shaped* have been applied The margins of these hemorrhages show an irregular or feathered edge When fresh their color is bright red but with age they darken to brown When there is partial obstruction to venous return through the central vein (as with papilledema) multiple hemorrhages of this type may closely surround the disk in radiating fashion

* Brust A A Retinopathies contrasted diagnostic and prognostic significance of the optic fundi in accelerated hypertension Am J Med 26 I 195[illegible]

HYPERTENSIVE HEMORRHAGES

The hemorrhages which are seen in association with advanced hyper tension are classically those of the nerve fiber layer type and may be of arterial venous or capillary origin Their configuration affords no clue to the underlying etiology of the elevated blood pressure however many observers believe that the mere appearance of hemorrhage suggests the acceleration of a previously benign hypertensive process Other disorders causing nerve fiber layer hemorrhage of course may afflict the hypertensive patient and therefore must be excluded

In accelerated hypertension hemorrhages may appear singly or in show ers and fresh ones often crop out while older ones are being resorbed Most commonly they are located within two or three disk diameters of the nerve head sparing the peripheral portions of the fundus Though they occur in greater profusion when papilledema co exists swelling of the nerve head is not a prerequisite for their appearance In some instances the proximity of hemorrhage to a nearby artery or vein may define the site of origin

EXUDATIVE CHANGES IN RENAL DISEASE AND HYPERTENSION

The varied exudative changes seen in the optic fundi represent different manifestations of the formation migration coalescence and resorption of retinal edema In acute active forms of renal disease (as acute glomerulo nephritis) white fluffy conglomerates of edema frequently localize in the nerve fiber layer These are commonly called *cotton wool patches* they vary from a pinpoint up to a disk diameter in size are irregular in shape and usually show furred or striated margins They are readily resorbable usually disappearing without residual in three to four weeks Solitary patches fre quently are situated at the bifurcations of retinal arteries

Offering sharp contrast to the soft fluffiness of the cotton wool patches are the discrete yellow and white *punctate exudates* which frequently be come widely distributed throughout the fundus in patients with chronic renal disease especially those with retinal vascular damage from hyperten sion These scattered lesions lie deep to the major retinal vessels and though potentially evanescent they disappear much more slowly than the cotton wool patches Their less rapid resorption most likely reflects a more severe degree of retinal ischemia

It must be remembered that transient edema residues of a highly mobile nature may be observed in the fundus when retinal edema and papilledema recede regardless of the underlying disease present Following the path described by the course of the nerve fibers the edema fluid is dispersed peripherally from the disk region

PAPILLEDEMA

In the hypertensive patient papilledema (grade IV fundi) has come to be regarded as the most consistently reliable sign that the disease has en tered an accelerated phase Implicit therein is the ominous prognosis of malignant" hypertension In this regard it must be remembered that papil ledema frequently is seen in conditions in which hypertension may be merely an associated concomitant (acute glomerulonephritis lead poisoning head

trauma pseudotumor cerebri) In addition certain complications which may befall the benign hypertensive patient can give rise to papilledema (spontaneous subarachnoid hemorrhage leaking berry aneurysm intracerebral hemorrhage) Obviously the success of management of the causative episode will be a better guide to prognosis in such instances than will the mere presence of papilledema

When swelling of the optic disk occurs as a manifestation of the course of hypertension only minimal signs and symptoms may be produced until the process becomes fully developed Loss of physiologic cupping blurring of disk margins and overfilling of the veins must be sought carefully if the diagnosis is to be made at an early stage It is generally agreed that the temporal margin of the disk is the last portion to become blurred

RETINOPATHY AND BLOOD PRESSURE LEVEL

Though high levels of diastolic blood pressure usually go hand in hand with the more severe grades of hypertensive retinopathy (grade III and grade IV) there has been no satisfactory demonstration that blood pressure height *per se* is responsible for the retinal changes except as it may reflect the severity of the underlying vascular disturbance Indeed advanced retinopathy sometimes may be absent in patients with extremely high diastolic levels and conversely severe retinal changes occasionally occur when the diastolic pressure is only slightly or moderately elevated To be sure such instances represent exceptions to the general rule but they emphasize the need for a clearer understanding of the natural history and reversibility of hypertensive retinopathy with respect to changes in blood pressure level

In our studies of patients in the accelerated phase of hypertension it was repeatedly noted that advanced retinopathy may appear and progress in spite of moderation of the blood pressure level Conversely regression of hemorrhages exudates and papilledema was seen to occur without lowering of blood pressure level even in the presence of advancing uremia

Since retinal ischemia plays a major role in the production of these more severe retinal manifestations the distribution of the retinal vessels the integrity of their lumina and the elasticity and permeability of their walls must be reckoned with along with hemodynamic considerations

Effect of Blood Pressure Reduction on Vascular Changes in the Eye*

WALTER M KIRKENDALL and MARK L ARMSTRONG

College of Medicine State University of Iowa

Two years ago we began a study of the changes in the optic fundi in hypertensive patients with and without therapy We proposed to correlate the vascular events in the fundus with changes in the remainder of the body particularly in systemic arterial blood pressure This permits accurate evaluation of current therapy directed to blood pressure lowering We hoped that the study might reveal changes which could be used as prognostic signs in the management of hypertensive patients

We took serial color photographs of the fundi and studied these for changes We considered a plan of serial funduscopic observations without photographs but rejected it because we found it to be less accurate Evelyn Nicholls and Turnbull[1] reached the opposite conclusion The photographs made it possible for us to demonstrate the results objectively

This is a report of the first 50 patients selected and studied for one year or until death Its purpose is to correlate the optic fundus vascular changes with the blood pressure changes as recorded over the one year period

METHODS AND MATERIALS

All our patients were men between the ages of 30 and 69 (average 54) on the medical wards of the Iowa City Veterans Administration Hospital All patients 69 years of age or under with a diastolic blood pressure average of more than 90 mm Hg on the fourth through the sixth day of hospitalization were selected if they did not have secondary hypertension and if they were willing to participate in the program

On the basis of a careful and complete examination cases were classified as mild moderate and severe Treatment schedules for the mild and moderate groups included placebos those in the severe did not A double blind plan of therapy for each patient was selected in a random manner Each was given equipment for recording his blood pressure and was taught to use it Except for the initial blood pressure values all pressures reported are averages of those the patient took four times a day for a year Arterial blood pressure is given as the mean pressure This was obtained by subtracting 5 from the pulse pressure dividing the difference by 2 and adding the observed diastolic pressure

Before therapy was started five photographs of each optic fundus (cen

*This study was supported by grants from the Veterans Administration and from the United States Public Health Service (No H 3270)

TABLE 1 ARTERIOLOSCLEROTIC CHANGES

GRADE		
0		Normal
I	a	Mild thickening of the arteriolar wall best noted by widening of the light reflex
	b	*And/or* slight depression of veins at the A V junction
II	a	More pronounced arteriolar wall thickening
	b	*And* almost complete invisibility of veins at the A V junction
	c	May have early copper color in arterioles
III	a	Above changes
	b	*Plus* complete invisibility of veins beneath A V junction
	c	*And* distal venous dilatation
	d	*And* usually copper and silver wire arterioles
IV	a	Above changes
	b	*Plus* arterial and venous obliteration
	c	Hemorrhages and exudates (rarely) *may occur secondary to retinal arteriolar and venular occlusion*

tral nasal temporal inferior and superior fields) were taken Photographs were taken again at six month intervals in the severe group and at yearly intervals for those in mild and moderate classifications Eighty per cent of the photographs were judged by us to be of good or excellent technical quality and adequate for interpretation

We used the classification in Tables 1 and 2 to grade the fundi This classification is a composite with minor modifications of that recommended by the Committee on Classification of Hypertensive Disease of the Retina of the American Ophthalmological Society and that suggested by Scheie[3]

We graded the fundic photographs soon after they were taken without knowing the identity of the patients or their response to therapy Later the photographs from the same patient taken at different times were collected and similar views from each patient were evaluated simultaneously After this grading was recorded the blood pressure averages were given to us and the correlations made We still do not know the specific drug or drugs used in each case

RESULTS

The results of our evaluation of the photos in the 44 patients living at the

TABLE 2 HYPERTENSIVE (ANGIOSPASTIC) CHANGES

GRADE		
0		Normal
I	a	Mild generalized narrowing (arterioles no narrower than [illegible] the calibre of veins)
	b	*And/or* sparse focal arteriolar constrictions (constricted areas being [illegible] the calibre of the proximal arteriolar segment)
II	a	Generalized narrowing (arterioles reduced to [illegible] the calibre of veins)
	b	*And* frequent focal constrictions ([illegible] the calibre of proximal arteriolar segment)
	c	Here definite irregularity of arterioles is easily noted
III	a	Generalized narrowing (arterioles reduced to [illegible] the calibre of veins)
	b	*And* focal constrictions ([illegible] the calibre of proximal arteriolar segment)
	c	*And* hemorrhages
	d	*And* usually exudates
IV	a	Generalized narrowing with threadlike or invisible arterioles
	b	*And* focal construction with narrowed areas invisible or nearly so
	c	*And* hemorrhages and exudates
	d	*And* papilledema

time of the second optic photograph can be seen in Figures 1 and 2 (p 476) and in Table 3

Figure 1 shows the change in mean blood pressure related to change in arteriolosclerotic grading In no instance did the rating change downward In seven patients there was a worsening in the arteriolosclerotic grade In two of the remaining 37 patients there was a questionable increase in arteriovenous nicking but this was not definite and all were listed as having no change in grade In those patients in whom a change was detected two had little change in blood pressure (+ 3 and + 3 mm Hg mean pressure) two had slight rises (+ 9 and + 12) and three had significant drops (− 14 − 49 − 35) This parallels the change in pressure of the group as a whole and suggests that retinal vascular changes go on even in the presence of significant blood pressure reduction

A different picture is seen in Figure 2 in which hypertensive fundic

TABLE 3 RETINAL VASCULAR AND BLOOD PRESSURE CHANGES IN HYPERTENSIVE PATIENTS

	Name	Age (Years)	Initial Mean Blood Pressure (mm Hg)	12 Month Mean Blood Pressure (mm Hg)	Difference in Mean Pressure (mm Hg)	Difference in Arteriolosclerotic Grade (Units)	Difference in Hypertensive Grade (Units)	Comments
1	A B	64	121	119	− 2	0	0	
2	G B	29	126	115	− 11	0	0	
3	B A	65	121	116	− 5	0	0	
4	B N	47	123	119	− 4	0	− 1	
5	D I	65	134	120	− 14	+ 1	0	
6	E W	62	123	147	+ 24	0	0	
7	G R	53	124	109	− 15	0	0	
8	H O	53	120	116	− 4	0	0	
9	L E	39	125	124	− 1	0	0	
10	L I	65	126	92	− 34	0	0	
11	M A	51	123	116	− 7	0	0	
12	O L	64	134	131	− 3	+ 1	0	
13	P O	59	117	131	+ 14	0	0	
14	R A	62	121	124	+ 3	+ 1	0	
15	R I	34	123	134	+ 11	0	0	
16	S A	61	141	142	+ 1	0	0	
17	S C	63	122	132	+ 10	0	0	
18	S L	42	123	112	− 11	0	0	
19	S W	69	121	112	− 9	0	0	
20	W A	68	124	136	+ 12	0	0	
21	C L	61	108	111	+ 3	0	0	
22	J O	46	119	106	− 13	0	0	
23	M S	34	127	106	− 21	0	0	
24	B I	51	179	119	− 60	0	− 1	
25	B L	57	114	126	+ 12	+ 1	− 1	
26	B R	62	122	107	− 15	0	0	
27	B V	65	142	139	− 3	0	0	
28	H A	60	116	105	− 11	0	− 1	
29	J E	39	127	105	− 22	0	− 1	
30	K E	69	146	155	+ 9	+ 1	− 1	
31	S T	64	134	130	− 4	0	0	
32	S A	58	143	129	− 14	0	0	
33	H U	69	167	140	− 27	0	− 1	
34	K L	66	127	109	− 18	0	0	

TABLE 3 RETINAL VASCULAR AND BLOOD PRESSURE CHANGES IN HYPERTENSIVE PATIENTS—(Continued)

	Name	Age (Years)	Initial Mean Blood Pressure (mm Hg)	1 Month Mean Blood Pressure (mm Hg)	Difference in Mean Pressure (mm Hg)	Difference in Arteriolosclerotic Grade (Units)	Difference in Hypertensive Grade (Units)	Comments
35	S P	31	171	158	−13	0	−1	
36	W E	64	149	114	−35	0	0	
37	M C	34	144	132	−12	0	0	
38	S H	64	174	125	−49	+1	0	
39	M R	56	143	108	−35	+1	−1	
40	B O	37	168	143	−25	0	0	
41	L N	41	128	170	+32	0	0	
42	D A	62	145	133	−12	0	+1	
43	F A	43	195	122	−73	0	0	
44	K I	38	198	122	−76	0	−2	
45	S C	65	150	120	−30			Died of myocardial infarction possibly precipitated by sharp fall in blood pressure (blocked) 2 months
46	T I	35	168	152	−16			Died of progressive renal disease 3 months
47	P A	58	157	158	+ 2			Died of myocardial infarction and rupture of heart 11 months
48	P R	62	134	148	+14			Died of myocardial infarction 14 months
49	H V	50	157	158	+ 1			Died of cerebral vascular accidents and progressive renal disease 5 months
50	N A	37	154	173	+19			Died of progressive renal disease 2 months
	Average age	54						

changes are compared to mean blood pressure changes Here there was only one increase in grade in a patient who was in the severe group and had a 12 mm Hg drop in mean pressure Thirty three showed no change and ten patients had a decrease in grade (nine of 1 + one of 2 +) Of these three had an insignificant fall or a moderate rise in pressure (− 4 + 12 + 9) and the chief increase when it occurred was in the systolic pressure The other seven had significant decreases in mean pressure (− 60 − 11 − 22 − 27 − 13 − 35 − 76 average 35)

This figure shows that decreases in hypertensive grade are somewhat more likely to occur with significant drops (over 10 mm Hg) in blood pressure In three of the patients there was clearing of the hypertensive changes but progression of the arteriolosclerotic ones These patients had mean blood pressure changes of + 9 + 12 and − 35 All were over 50 years of age

Of the original 50 patients six (Table 3) died in two to 14 months three of myocardial infarction two of progressive renal disease (both had had BUNs of over 90 mg per cent on admission) and one of repeated cerebral vascular accidents and progressive renal disease

Figures 3 to 12 demonstrate some of the changes we saw and some of the features which were difficult to evaluate

Change in **Mean Blood Pressure** During the Year
and Change in **Optic Fundus Grade** at End of the Year

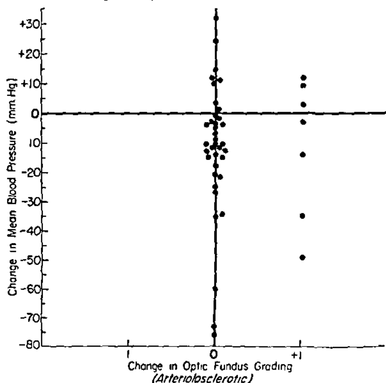


Fig 1

Change in **Mean Blood Pressure** During the Year
and Change in **Optic Fundus Grade** at End of the Year

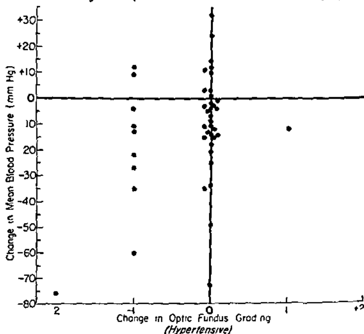


Fig 2

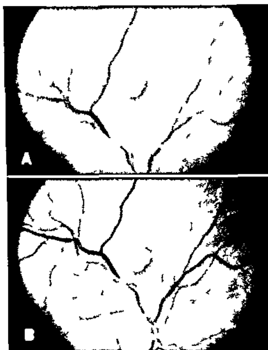


Fig 3 Patient O L The lower photograph taken after one year of observation shows a generalized increase in arteriolar size

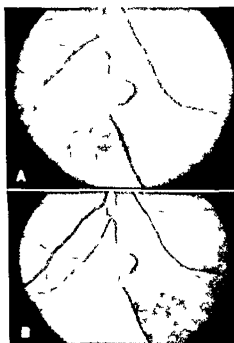


Fig 4 Patient J E The lower photograph, taken one year after the upper shows a generalized increase in arteriolar calibre

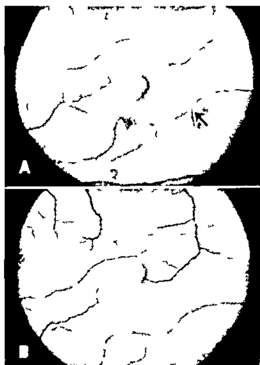


Fig 5 Patient B I The area of local constriction seen in the first photograph has relaxed in the second taken one year later Hemorrhages and exudates also have cleared

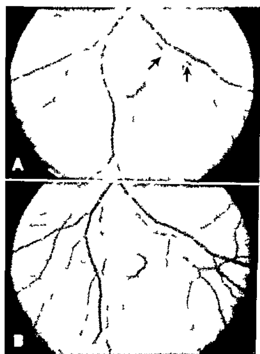


Fig 6 Patient H A The areas of local constriction in the upper photograph have relaxed to a considerable degree in the lower taken one year later

Was there a demonstrable increase in the size of small blood vessels in some patients?

This question is a difficult one to answer with certainty because minor differences in photographic technique can cause apparent changes in vessel diameter For this reason we did not alter the hypertensive grade of any patient when this was the only change We do believe that there was a distinct increase in the size of small blood vessels usually as pressure was lowered

Figures 3 and 4 are paired photographs taken one year apart of the retinas of two patients (O L and J E) The patient shown in Figure 3 had a fall in mean blood pressure of 5 mm Hg and the patient in Figure 4 a fall of 22 Both show the degree of increase in arteriolar size which we observed several times

Can angiospastic constricted areas be released?

By implication or direct statement most authors[1] writing on optic fundus changes in chronic hypertensives agree that this can occur usually with pressure drops although all do not agree on this point[8, 9] There is no doubt that such spastic areas relax when *acute* hypertension is lowered

Figures 5 and 6 each show in the one year photograph at least one instance in which a localized spastic area has disappeared Mean blood pressure fell 60 and 11 mm Hg respectively during the year

What happens to localized constriction secondary to arteriolosclerotic changes?

We think that these constrictions remain without change or become more severe even when blood pressure lowering is pronounced In the examples illustrated by Figures 7 8 and 9 however blood pressure stayed about the same throughout the year

A problem closely related to the state of localized sclerotic areas is that of arteriolovenular nicking We saw many A V crossing phenomena which seemed to become more pronounced after one year and none improved regardless of significant change in blood pressure (Figs 10 and 11)

Figures 11 and 12 are retinal photographs of a patient (M C) who had a mean blood pressure fall of 35 mm Hg with clearing of the hypertensive retinopathy (Fig 12) He also had (Fig 11) progression of the sclerotic changes at the arteriovenous junction so that venular occlusive hemorrhages occurred

This dichotomy between hypertensive and arteriolosclerotic vascular changes occurred in two other patients in this series and we have seen it a number of times in other patients

DISCUSSION

This study is of short duration and is not yet complete More patients must be followed longer before results can be significant It is further limited in its significance because it deals only with men many of whom were relatively old However if these objections are kept in mind certain trends are worthy of mention

1 Whether blood pressure is lowered or not arteriolosclerotic changes continue to appear in the optic fundus Changes for the worse occur in arteriolar thickening (and probably tortuosity) arteriolar venular crossing phenomena and atherosclerotic plaques

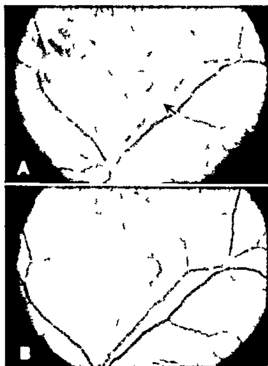


Fig 7 Patient A B Persistence of area of localized narrowing caused by arteriolosclerosis in the lower photograph taken one year after the upper one

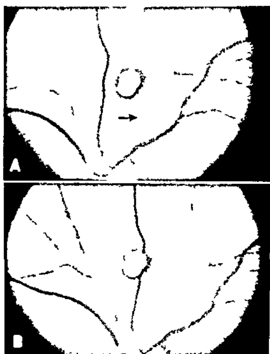


Fig 8 Patient B L Progressive obliteration of an arteriole after one year



Fig 9 Patient R A Increase in size of atherosclerotic plaque in one year The vessels involved are probably small arteries rather than arterioles [11]



Fig 10 Patient B V Suggestive increase in arteriovenous nicking after one year of observation The widening of the white area on the distal side of the arteriole could be an artifact caused by a different camera angle but is probably real. There is also progressive obliteration of the arteriole in the lower right quadrant

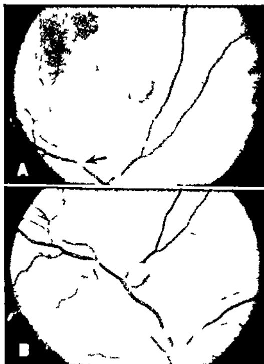


Fig 11 Patient M R Progression of arteriovenous crossing defect with development of hemorrhages caused by venous obstruction in the area drained by venule under the arteriole

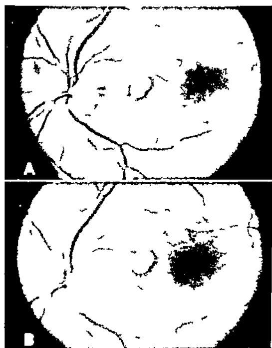


Fig 12 Same patient as in Figure 11 Note the disappearance of hypertensive retinopathy in the year end photograph

2 If blood pressure is lowered and less frequently if it is not hypertensive retinopathy with papilledema hemorrhages and exudates regularly disappears Localized areas of constriction can be relaxed with effective therapy Probably generalized arteriolar constriction also decreases when blood pressure falls but measurement of this is very difficult by this method In our group of photographs we thought that constriction became worse in only two patients (both of whom had increase in blood pressure) while in six others we considered the vessels to be more prominent (five of these had falls between 5 and 22 mm Hg one had a 12 mm Hg increase)

The classification of the optic fundus vascular changes suggested by Scheie[3] was based on the assumption that the arteriolosclerosis seen was an index of the duration of hypertension the angiospastic changes a better index of its magnitude We have used this classification because it separates lesions which regressed (hypertensive) from those which remained the same or became worse (the arteriolosclerotic) when effective hypotensive therapy was achieved The point of interest is not that the angiospastic changes often receded when blood pressure was lowered but that the arteriolosclerotic lesions sometimes progressed. This progression may be caused by the closing off of vessels from lowered arteriolar blood pressure or to extension of changes in the endothelium which originally narrowed them If it is from the loss of pressure a longer period of observation should demonstrate a tapering off in the frequency of this sign of increased damage if it is from endothelial proliferation the lesions will continue to appear despite blood pressure lowering In either case separation of the hypertensive and arteriolosclerotic lesions appears to be significant from a pathogenetic as well as from a clinical standpoint

Progression of atherosclerotic lesions in well treated hypertensive patients has been reported [10] Our study shows that similar obliterative changes occur in arterioles under the same conditions These results point out a major defect in current methods of treatment for the hypertensive Whether this defect can be obviated by earlier blood pressure reduction or whether it can best be treated by an entirely different approach is a problem of major importance

SUMMARY AND CONCLUSIONS

1 Retinal photographs of 44 patients were taken before and after one year of treatment The changes in the retinal vessels were compared to changes in mean blood pressure

2 There was an increase in retinal arteriolosclerotic grade in seven patients three of whom had significant drops in mean blood pressure

3 Ten patients had a decrease in retinal hypertensive (*angiospastic*) grade most with sharp falls in mean blood pressure One patient, who had a 12 mm Hg fall in mean blood pressure had an increase in hypertensive grade

4 Three patients had an *increase* in retinal arteriolosclerotic grade and a *decrease* in hypertensive grade

5 The progression of sclerosing lesions in arterioles in patients with adequate blood pressure reduction emphasizes a defect in current methods of treatment.

ACKNOWLEDGMENTS

The retinal photographs used in this study were taken by Mr Lee Allen and Mr Howard Webster of the Department of Ophthalmology College of Medicine State University of Iowa We wish to express our appreciation to these men for their encouragement and advice

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The Effect of Blood Pressure Control on Renal Vascular Damage Associated with Hypertension*

JOHN H MOYER

Hahnemann Medical College and Hospital

Extensive observations by numerous investigators have shown that the renal vascular system is usually damaged by the hypertensive process[1-6] The reduction in glomerular filtration rate and renal blood flow is proportional to the severity and duration of the sustained blood pressure elevation We have done differential renal function studies on 64 patients on whom similar observations had been made two to five years previously Of these 45 were treated adequately for their hypertension whereas the other 19

* Much of the material in this report is based on a previous report by Moyer *et al* Am J Med *34* 164 1958

were untreated This report compares the control and follow up renal function studies in patients with hypertension before and after treatment with that group of patients in whom hypertension was not treated Twenty one patients with malignant hypertension and five patients in whom one renal artery was occluded were studied also and these data were analyzed separately

METHODS

The patients with essential hypertension who were used in this study were picked at random from a group of patients seen at the Houston City County Hospital Hypertensive Clinic over a six year period from 1951 to 1956 All patients had a sustained elevation of the blood pressure above 150/100 mm Hg in both the supine and upright positions during a control observation period of three to four weeks while receiving placebo therapy None of the patients had evidence of primary renal disease

On the initial visit to the clinic a complete history was obtained and a physical examination was performed In addition certain routine laboratory examinations were obtained complete blood count urinalysis blood urea nitrogen determination electrocardiogram and x ray of the chest Each patient was started on a placebo regimen and blood pressure determinations were made with the patient in both the supine and upright positions once or twice a week for a period of three to four weeks The glomerular filtration rate (inulin clearance) and the renal plasma flow (clearance of para aminohippurate) were determined during this observation period The renal blood flow was calculated from the renal plasma flow The techniques and analytical procedures of the clearance tests have been described previously[6 7 8] These observations served as control values in the study Repeated renal function studies were performed during the follow up period The last follow up observations are the ones used for analysis of data in this study The duration of the follow up period ranged from two to five years Blood urea nitrogen determinations electrocardiograms and x rays of the chest were obtained immediately prior to the follow up renal function studies and are the ones presented in this study Forty five of the patients obtained a significant reduction in blood pressure throughout the follow up period This is defined as a reduction in the mean blood pressure (diastolic + ⅓ pulse pressure) of 20 mm Hg or more or a return to normotensive levels Nineteen patients had not had treatment of their hypertension either because effective drugs were lacking at the time or because they moved from the area and did not continue therapy or they voluntarily discontinued their medication before an effective therapeutic program was established

The antihypertensive therapy for the patients with essential hypertension varied in this study During 1951 and 1952 therapy consisted primarily of ganglionic blockade with hexamethonium These patients continued to receive a combination of Rauwolfia with a ganglionic blocking agent which during the last three years was either pentolinium (Ansolysen) or mecamylamine (Inversine) Methods and techniques employed when administering these drugs have been reported previously[9 14] About 10 per cent of the patients in this study received a combination of Rauwolfia with hydralazine (Apresoline) for variable periods of time This combination was not continued because it proved inadequate for long term blood pressure control

TABLE 1 VITAL STATISTICS AND CLINICAL OBSERVATIONS PRIOR TO THERAPY

DATA	GROUP I (DIASTOLIC PRESSURE < 130 MM HG)				GROUP II (DIASTOLIC PRESSURE > 130 MM HG)			
	TREATED		UNTREATED		TREATED		UNTREATED	
VITAL STATISTICS AND OBSERVATIONS ON BLOOD PRESSURE								
No of patients	14		8		31		11	
Per cent of total	22		13		48		17	
Average age	50		48		49		44	
Men	8		4		15		9	
Women	6		4		16		2	
White	5		0		14		6	
Negro	9		8		17		5	
Blood pressure supine								
Average systolic	212		179		226		242	
Average diastolic	122		117		143		155	
Average mean*	152		138		170		184	
Blood pressure upright								
Average systolic	209		175		224		231	
Average diastolic	123		122		147		158	
Average mean	152		140		173		183	
COMPLICATIONS OF HYPERTENSION IN PATIENTS PRIOR TO THERAPY								
	NO	%	NO	%	NO	%	NO	%
No of patients	14		8		31		11	
Abnormal urine	3	21	5	62	23	74	10	91
Abnormal electrocardiogram	8	57	4	50	26	84	10	91
Abnormal x ray†	5	36	4	50	25	81	10	91
Previous infarction	0	0	0	0	2	6	0	0
Previous cerebrovascular accident	3	21	1	13	5	16	2	18
Funduscopic								
Grades 1 and 2	11	79	6	75	13	42	2	18
Grades 3 and 4	3	21	1	13	18	58	9	82
Heart failure								
Class I	5	36	0	0	8	26	0	0
Class II	2	14	1	13	3	10	0	0
Class III	0	0	3	37	5	16	3	27
Class IV	0	0	0	0	1	3	0	0

* Mean blood pressure (diastolic + ⅓ pulse pressure)
† Refers to abnormalities of heart only

RESULTS

In Table 1 are presented the pretreatment vital statistics renal functional status and complications of hypertension in the 64 patients in whom we were able to perform follow up renal function studies The patients have been divided into two groups on the basis of the control diastolic blood pressure elevation Group I contains patients with mild to moderate hypertension (diastolic less than 130 mm Hg) and group II contains patients with more severe hypertension (diastolic greater than 130 mm Hg) These groups are further subdivided into treated and untreated patients There was no significant difference in the control renal functional status between treated and untreated patients within a group prior to starting therapy However,

there was a significant difference between the renal functional status of patients with mild to moderate hypertension and those with severe hypertension (Table 1) the latter having a significant reduction in function at the time the control observations were made Patients with severe hypertension (diastolic greater than 130 mm Hg) had a higher incidence of complications (Table 1) but again there was little difference between treated and untreated patients within each group during the control observation period Thus the status of the treated and untreated patients in each group prior to therapy was comparable

In Figures 1 and 2 there is a comparison of the renal functional status

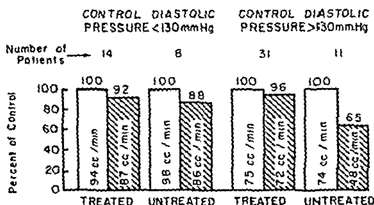


Fig. 1 Comparison of average control and 2 year (or more) follow up observations on glomerular filtration rates in treated and untreated patients with hypertension

during the follow up period as compared to the control period in treated and untreated patients of both groups I and II There was no significant difference in glomerular filtration rate in treated and untreated patients in group I (mild to moderate blood pressure elevation) when the control period and follow up period were compared The average follow up period was 28 months for the group The untreated patients in this group (group I) with mild to moderate hypertension showed a reduction in renal blood flow from 966 cc /minute to 755 cc /minute but otherwise no significant change occurred The mean blood pressure for the treated patients before and after treatment was 152 mm Hg and 114 mm Hg respectively ($p<0.001$) This compares to 140 mm Hg and 141 mm Hg in the untreated patients The degree of blood pressure control was as follows Of the 14 patients in group I who were treated the average upright diastolic pressure during the treat

ment period was less than 100 mm Hg in all but two patients In the two exceptions it was 110 and 113 mm Hg

In the 31 treated patients in group II (patients with severe hypertension) there was no change in renal function before and following treatment although the mean blood pressure was reduced from 173 mm Hg to 120 mm Hg (p<0 001) during a follow up period of 26 months The upright diastolic blood pressure during therapy was less than 100 mm Hg in 15 patients between 100 and 120 mm Hg in 14 patients and between 121 and 130 mm Hg in two patients There were no patients in whom the diastolic blood pressure was more than 130 mm Hg during therapy The untreated

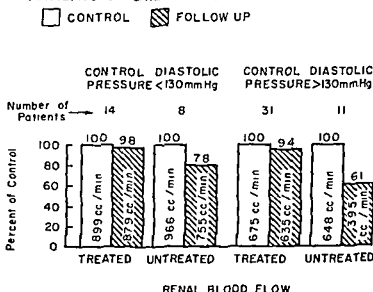


Fig 2 Comparison of average control and follow up observations on renal blood flow in treated and untreated patients with hypertension

patients in this group showed a marked reduction in function over a follow up period of only 24 months The control glomerular filtration rate and renal blood flow in these patients were 74 cc/minute and 648 cc/minute respectively compared to 48 cc/minute (p<0 01) and 395 cc/minute (p<0 01) for these functions at the time of the follow up observations on renal function In addition there was a slight rise in the mean blood pressure from 183 mm Hg to 192 mm Hg Treated patients in both groups showed a significant improvement in electrocardiographic changes and a decrease in size of the heart by x ray

The prognosis of hypertensive patients based upon the glomerular filtration rate prior to therapy is shown in Table 2 One hundred and sixteen patients* on whom renal clearance studies were performed and who could

* Follow up renal function studies were done on only 64 of these patients

TABLE 2 PROGNOSIS OF HYPERTENSIVE PATIENTS BASED ON GLOMERULAR FILTRATION RATE

GLOMERULAR FILTRATION RATE (CC /MIN)	NO OF PATIENTS		MORTALITY			
	TREATED	UNTREATED	TREATED		UNTREATED	
			NO	%	NO	%
>100	19	14	2	10	5	36
80 99	15	9	2	13	3	33
60 79	16	12	3	19	6	50
40 59	5	10	1	20	10	100
<40	7	9	3	43	9	100
Total	62	54	11	18	33	61

be followed *clinically* for three years have been divided into five groups according to initial glomerular filtration rate Each of these groups is divided into treated and untreated patients and the number and per cent mortality calculated for both treated and untreated patients These results show that the mortality increases and the prognosis becomes worse as the glomerular filtration rate decreases This is true in both treated and untreated patients However untreated patients show a much higher mortality than treated patients in each group The mortality in untreated patients with a glomerular filtration rate below 60 cc /minute was 100 per cent as compared to a mortality of less than 40 per cent in treated patients Over all the mortality for treated patients in this series was 18 per cent compared to 61 per cent in untreated patients

In Table 3 21 patients with malignant hypertension with control and follow up renal function studies are compared These patients were analyzed separately only to point out the rapid progression of this disease Of the 21 patients 12 patients were treated and nine were untreated Only two of the 12 treated patients have died to date and the average follow up period for the entire group of 12 is now 29 months All nine of the untreated patients have died the average survival time was 12 months The renal functional status of the 12 treated patients did not change over a follow up period averaging 28 months although the mean blood pressure was effectively

TABLE 3 COMPARISON OF FOLLOW UP RENAL STATUS IN TWENTY-ONE TREATED AND UNTREATED PATIENTS WITH MALIGNANT HYPERTENSION

DATA	TREATED		UNTREATED	
	NO	%	NO	%
Patients	12	57	9	43
Mortality	2	17	9	100
Survival time or follow up period if living	29 mo		12 mo	
Average	C	D	C	D
Blood urea nitrogen (mg %)	31	27	29	106
Glomerular filtration rate (cc /min)	66	68	70	44
Renal blood flow (cc /min)	513	579	628	351
Mean blood pressure (mm Hg)	175	122	184	197
Duration (C – D)	28 mo		10 mo	
Improved (%)				
Urinalysis	26		0	
Electrocardiogram	54		0	
X ray	54		0	

reduced from 175 mm Hg to 122 mm Hg In contrast to this the renal function of the nine untreated patients was reduced to approximately 60 per cent of control values ($p<0.01$) following a period of only ten months The mean blood pressure in this untreated group increased from 184 mm Hg to 197 mm Hg and the blood urea nitrogen from an average value of 29 mg per cent to 106 mg per cent In the treated patients there was improvement in the urinary findings electrocardiograms and size of the heart ranging from 26 per cent to 54 per cent of those who had abnormal findings initially None of the patients in the untreated group showed improvement in these abnormal findings

DISCUSSION

The results clearly demonstrate the value of effective treatment of hypertension in arresting renal vascular deterioration associated with this disease This fact is clearly demonstrated by the patients in group II These patients had severe hypertension as judged by the control diastolic blood pressure elevation and, when untreated showed a decline in glomerular filtration rate (Figure 1) and renal blood flow (Figure 2) to approximately two-thirds of the control value This was associated with a rising blood pressure and blood urea nitrogen In contrast the treated patients had a very satisfactory decrease in blood pressure and showed no deterioration in renal function It should be emphasized that there was usually no improvement in renal functional status in this group and it never returned to normal The effect of treatment was only to arrest the vascular deterioration observed in those patients who were treated Similar observations have been made by Perry and Schroeder [1] As a matter of fact one might anticipate that no significant improvement in function would occur in patients with slowly progressing renal damage since the injured nephrons are slowly replaced by scar tissue However in patients experiencing renal damage due to severe hypertension of relatively acute onset some improvement in renal function was sometimes observed when the blood pressure was reduced effectively and without delay (Fig 4)

In patients with mild hypertension there was no difference in vascular deterioration in the treated and untreated patients such as was observed in the severe cases probably because of the slower rate of renal deterioration in such patients which requires a longer period of time for demonstration than our follow up period of two to five years The fact that there was no significant difference in renal functional status between treated and untreated patients with mild to moderate hypertension (other than mild depression in the renal blood flow) should not lead the therapist to question the efficacy of treatment in this type of patient since the transition from normal to abnormal renal function does occur somewhere in the course of the disease in patients with hypertension of this severity [6] and since neither the treated nor the untreated patients in group I had normal clearance values at the time the control observations were made This indicated that some renal deterioration had already occurred This has been concluded by other members of this symposium also In our present state of knowledge we cannot say at what point the transition occurs The evidence suggests however that the higher the blood pressure the greater the degree of renal

damage Since it has been demonstrated that deterioration of renal function can be arrested by treatment in severe cases it seems only reasonable to suppose that early treatment of the mild and moderately severe case would be of even greater value in delaying or preventing the vascular deterioration in the kidney The slow progression of the disease process in these patients can be used to advantage by the clinician for it is in this type of patient that the blood pressure can be reduced gradually and much more effectively over a longer period of time thereby preventing some of the untoward reactions to rapid reduction of the blood pressure Finally there is evidence to indicate that improvement occurs in the electrocardiogram

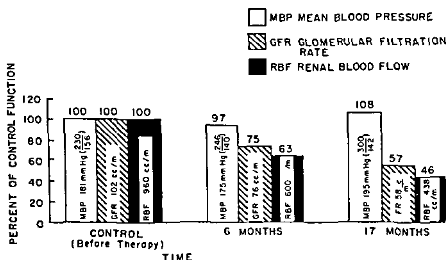


Fig 3 A patient with malignant hypertension who was not treated for a period of seventeen months There was progressive reduction in glomerular filtration rate and renal blood flow A few weeks after the last renal function test was performed the patient died of congestive heart failure and renal failure (From Am J Med 34 164 1958)

associated with a decrease in heart size of the treated patients not only in those with severe hypertension but in patients with mild type hypertension as well

An additional reason for active and early treatment of patients with hypertension is presented in Table 2 As the glomerular filtration rate decreased a reflection of vascular deterioration there was an increase in mortality in both treated and untreated patients The mortality rate in untreated patients was three times that of the treated patients The results indicate that treatment by arresting renal deterioration will keep a patient from falling into a group with a lower renal function and hence a worse prognosis Secondly once a patient is in a lower function group his prognosis is better with than without treatment (Table 2)

Further evidence for effective treatment is obtained when the results in treated and untreated patients are compared in the entire group of 116 patients studied initially with all grades of severity Seventy five per cent of the patients who died were untreated None of the patients who were treated died of uremia as the sole cause of death This is in contrast to 15 untreated patients who died in uremia Five of the nine treated patients who

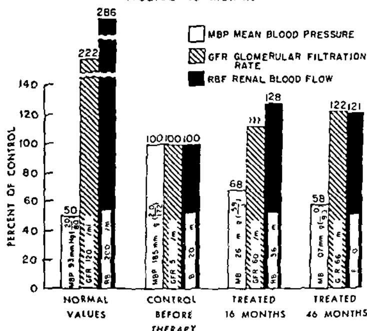


Fig 4 Summary of results in a patient with malignant hypertension who was treated effectively with antihypertensive agents (Rauwolfia plus ganglionic blockade) Prior to the institution of therapy the glomerular filtration rate and renal blood flow were depressed to less than 50 per cent of normal because of the vascular deterioration associated with malignant hypertension However following effective antihypertensive therapy for a period of four years there was no further reduction in glomerular filtration rate and renal blood flow This indicates that the vascular deterioration associated with malignant hypertension can be arrested by effective antihypertensive therapy (From Am J Med 34 164 1958)

died as a result of cerebral vascular accidents had had effective treatment and control of their blood pressure but then voluntarily discontinued treatment All five were dead in less than three months after discontinuation of their medication Unfortunately we have blood pressure observations on only three of these patients after they discontinued treatment In all three a sudden rise in blood pressure occurred shortly thereafter and this presumably resulted in hemorrhage into the brain The same sequence of events probably occurred in the other two patients These cases illustrate not only the value of antihypertensive treatment but also the importance of maintain

ing treatment once it has been started Sudden withdrawal of drugs is as disastrous as no treatment at all

The value of treatment is clearly shown in 21 patients with malignant hypertension who had follow up renal studies In the treated patients the renal deterioration was arrested in association with a significant reduction in mean blood pressure from 175 mm to 122 mm Hg for the group over a follow up period of 28 months This is in contrast to the decrease in function in untreated patients (Table 3) Patient J E (Fig 3) is a typical patient with malignant hypertension who was not treated The progressive renal vascular deterioration is evident By contrast patient T H (Fig 4) was treated and the renal vascular deterioration was arrested

The patient presented in Figure 3 who suffered from malignant hypertension was a 38 year old white man with a control blood pressure of 230/156 mm Hg His control renal clearances were only slightly below normal He received no treatment six months later his renal function was approximately 70 per cent of control values and his blood pressure remained elevated Seventeen months after the control observations his blood pressure was still elevated and his renal function had dropped to around 50 per cent of control values This patient died a few weeks later in congestive heart failure

The patient in Figure 4 also suffered from malignant hypertension When first seen in the clinic he had a pressure of 210/172 mm Hg and his renal function was about 50 per cent of normal He was given antihypertensive therapy and experienced a fall in blood pressure in 16 months to 158/110 mm Hg His renal function at that time was slightly better than during the control observations but had not changed significantly Forty six months after treatment began the blood pressure had been reduced to normotensive levels (140/90 mm Hg) and his renal functional status remained stable This patient is still alive and gainfully employed

Patients with unilateral renal arterial occlusive disease demonstrate clearly that renal disease can produce hypertension and that the hypertension can in turn produce renal damage (Table 4) Good evidence for the renal origin of hypertension was presented by the first two patients in Table 4 who became normotensive following nephrectomy The glomerular filtration rate and renal blood flow were moderately depressed in the unoccluded kidney in Case I apparently as a result of the hypertensive process When the blood pressure returned to normal renal function in the unoccluded kidney improved dramatically returning to normal Similar observations were made in three additional patients two of whom (Cases IV and V) were treated with medical therapy only Nephrectomy was performed in the third patient but the blood pressure remained elevated Medical antihypertensive therapy was required following which the blood pressure was reduced and renal function improved The observations on these five patients support the concept that severe hypertension alone can produce generalized vascular damage frequently most marked in the kidneys since vascular deterioration was observed in the contralateral kidney in which the blood supply was not altered but the arterial blood pressure was elevated Furthermore the vascular degenerative changes were not only arrested by reducing the blood pressure but blood pressure reduction by any means was accompanied by an improvement in renal function

TABLE 4 OBSERVATIONS ON CONTRALATERAL KIDNEY IN PATIENTS WITH UNILATERAL RENAL ARTERY OCCLUSION

CASE NO	THERAPY FOR HYPERTENSION	GLOMERULAR FILTRATION RATE (CC/MIN)		RENAL BLOOD FLOW (CC/MIN)		BLOOD UREA NITROGEN (MG %)		UPRIGHT BLOOD PRESSURE† SYSTOLIC		UPRIGHT BLOOD PRESSURE† DIASTOLIC		TIME INTERVAL‡ MONTHS	RESULTS
		C	D	C	D	C	D	C	D	C	D	D_1	
I	Nephrectomy	36	63	195	666	48	16	270	132	192	90	28	*Died ruptured homograph*
II	*Nephrectomy*	55	80	744	940	18	18	244	160	156	96	18	Living and well
III	Nephrectomy Rauwolfia plus pentolinium	20	54	110	480	82	36	210	160	168	90	36	Living and well
IV	Rauwolfia plus *pentolinium*	46	58	420	440	32	28	196	130	142	100	19	Died after 2 years coronary occlusion
V	Rauwolfia plus mecamylamine	25	56	*130*	*650*	*70*	*36*	*230*	*150*	*160*	92	24	Living *and* well

The ureter to the occluded kidney was catheterized in each patient but there was no urine formation consequently *renal function* could not be measured

† Retinal hemorrhages and papilledema were present in all five patients

‡ Period of time between control observation and follow up observation on renal function

C Control

D Observation after therapy was instituted

SUMMARY

Renal clearance studies were performed in patients with hypertensive vascular disease employing serial renal function studies Forty five of 64 so studied were treated and 19 were untreated

Comparison of treated and untreated patients showed that effective reduction of the blood pressure arrested the renal vascular deterioration associated with hypertension in patients with severe and moderately severe hypertension Untreated patients with mild and moderately severe hypertension did not show the rapid renal deterioration that occurs in patients with more marked elevation of the blood pressure

The mortality was significantly lower in treated patients than in untreated patients Renal deterioration was arrested and mortality reduced in patients with malignant hypertension who were treated

Five patients with hypertension due to unilateral renal artery occlusion were studied Glomerular filtration rate and renal blood flow were reduced significantly in the contralateral kidney as a result of the severe hypertension exhibited by these patients This vascular deterioration in the unoccluded kidney could be arrested and was partly reversible when the blood pressure was reduced effectively These results indicate that renal deterioration can be arrested by effective treatment of hypertension and that the lives of hyper tensive patients can thus be prolonged It is recommended therefore that hypertensive vascular disease be treated vigorously and early in the hope of decreasing the morbidity and mortality which too commonly result from this disease

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Discussion

GARFIELD DUNCAN *Moderator*

BENEDICT ABREU	SIBLEY HOOBLER
ALBERT BRUST	WALTER KIRKENDALL
RICHARD DUNSMORE	EDWARD MEILMAN
RALPH FORD	MILTON MENDLOWITZ
EDWARD FREIS	JOHN MOYER
ARTHUR GROLLMAN	WILLIAM PATON
CAROLL HANDLEY	H MITCHELL PERRY
WILLIAM HOLLANDER	ALBERT PLUMMER

DR DUNCAN I think that one of the most important questions that would arise out of these papers is *when to treat hypertension* In view of the fact that Dr Moyer showed an arrest of the vascular changes with therapy it seems to me that he would be a good one to answer this question When and at what degree of hypertension should we advocate treatment?

DR MOYER If I may make a generalization I would say that the higher the diastolic pressure and the higher the incidence of complications associated with hypertension the greater the indication for effective reduction of blood pressure By contrast antihypertensive drugs may be held in abeyance in the patient who has a labile blood pressure i e whose diastolic pressure is only occasionally above 100 mm Hg but many times is found to be 90 to 95 I would recommend that a physician follow this patient carefully and when there is evidence of progression this then is the time to start therapy This doesn t give many details but I think that these are the generalizations that can be drawn

DR DUNCAN A question would arise Is not hypertension of any severity likely to start in the labile form? Therefore when recognized in its early phases would treatment not be indicated?

DR. MOYER I think that probably all patients with hypertension even severe hypertension arise from a group which at some time have a milder disease On the other hand there is an adequately large group of patients

particularly women who have labile hypertension which exists for many years without complications Because of the problems associated with anti hypertensive therapy such as drug idiosyncrasies etc I would think that in this group of patients it would be well worth while following them along without giving them drugs rather than starting antihypertensive therapy without further ado From the observations that we were able to make on renal function the patients who had diastolic arterial pressures below 110 mm Hg and those in whom the diastolic pressure dropped below this level on many occasions didn t show significant evidence of vascular deterioration over a three year follow up period i e comparing the treated and untreated patients

Dr Duncan Do any other members of the panel have any comments to make on these principles?

Dr Hollander Although antihypertensive drug treatment may not have a pronounced effect on the arteriosclerotic lesions it is possible that it might have a more evident effect in preventing atherosclerosis that is preventing coronary artery disease which actually is one of the major causes of death in arterial hypertension

Dr Duncan Any further comments?

Dr Freis I would agree with Dr Moyer and maybe put in a few provisos These are that we need to consider also the age of the patient and the sex of the patient The younger the patient the more one would be tempted to treat mild hypertension and also one would be more tempted to treat the male patient than the female patient at any given level of blood pressure because in general the male develops organic damage more quickly

Dr Duncan Another question that I have here deals with renal biopsies Of what assistance are these?

Dr Freis Dr Parrish did these at our hospital a number of years back and he gave them up because he ran into so much trouble with hemorrhage in the hypertensive kidney that he decided that it was too dangerous a procedure i e in the hypertensive

Dr Duncan I would like to ask Dr Hoobler who has had some experience with the two or three new ganglionic blocking agents are they to be preferred? Would he select either one of them over mecamylamine let us say?

Dr Hoobler I have had very little experience with any of them except trimethidinium and I think that you pay your money and take your choice If you want blurred vision at the expense of less constipation and if your hypertension is reasonably mild trimethidinium is effective therapy On the other hand if the constipation isn t very bad while taking mecamylamine and the pressure is quite high mecamylamine is the drug of choice We found it difficult to get good control of blood pressure in patients with severe hypertension when we converted from mecamylamine to trimethidinium

DR DUNSMORE Trimethidinium has been advocated by some as being a drug which has in addition to its ganglionic blocking effect peripherally a central action It isnt strange that ganglion blocking drugs should also have a central action because by ganglion block they also effect the brain as well but it is very hard to prove We did in acute study showing that there was a secondary drop in blood pressure from the fourth to the eighth hour after the administration of this drug intravenously That is in the first hour there was a sharp drop in pressure and then in the fourth to the eighth hour we were also able to show an additional effect We werent able to show any real bradycardia which we thought might be some evidence of central action and we saw no unusual psychic effects which we were also looking for although one or two patients did impress us as being rather tranquil during the height of the hypotensive effect I might also add that in cross circulation experiments in animals trimethidinium very definitely has an effect on the receptor

DR PATON I just might make two comments here First when you have a quaternary salt it is rather unlikely that it will get through to the brain I have tested this very vigorously with some of them and got less than 1 per cent of the plasma level obtaining in the cerebral spinal fluid The second reason is of course that ganglion blocking agents in general are competing with acetylcholine so that the only neural structures that you would expect them to act on would be cholinergic ones within the brain Theres only one certain cholinergic transmission in the spinal cord This is a cell most people dont know anything about which is a cell found in association with the anterior horn cells Really the acetylcholine transmission in the brain is a very uncertain proposition That being so it is extremely hard to associate any ganglionic actions with any definite central action I would like to illuminate my prejudices a bit further by saying that I personally believe that we need four central transmitters not one and that the assumption that acetylcholine mediates all our nervous activity is almost certainly an incorrect one This is the background to my reluctance to accept a central action but of course if it were proved to be so then one would adjust ones ideas

DR HOOBLER I think that the intravenous injection of trimethidinium far outlasts anything you would predict from the response following oral administration as if some component of the drug action is being blocked out by the liver after oral administration A single intravenous injection of 1 mg has been noted to keep the blood pressure down for over 12 hours Assuming 5 per cent absorption we certainly see nothing like that when we give a single 20 mg dose orally The reason I bring this up is that the company is advertising that this can be given parenterally and they are talking about 3 mg doses We nearly had a patient expire following a 3 mg dose He was hypotensive for two and a half days and anuric until we got his blood pressure up with norepinephrine So I think there is a real risk following parenteral use in any but the very smallest amounts

DR KIRKENDALL I quite agree with you We didnt use over 3 mg at any time and used 3 mg only in the younger more vigorous patients They often would have orthostatic hypotension of a rather severe degree for 24 hours

DR. DUNSMORE: We have been doing blood levels with trimethidinium and we have seen blood pressure effects at blood levels between 2.5 mcg. to 5 mcg. 12 hours following a single oral dose of 40 mg. Our group of 38 patients have been followed on oral medications for an average of 12 months and I agree with everything that has been said with regard to the potential advantages or disadvantages. Occasionally you will find a patient who will respond better to one of the blocking agents as compared to another. Perhaps it's because he has less parasympathetic blockade and therefore he sticks to his dosage regimen better. Beyond that we have also done spinal fluid levels and we get no appreciable trimethidinium in the spinal fluid. It is true that it does not appear in the spinal fluid.

DR. DUNCAN: I wonder if some other member of the panel would tell us as practicing physicians the indications for ganglion blocking agents. We all see patients come into the hospital who have received such agents and who should not have received them. Have you some rule of thumb? We use the Sodium Amytal test. Dr. Grollman, would you like to comment?

DR. GROLLMAN: That's a hard question, Dr. Duncan. I was trying to escape it. I would say only use them when you couldn't get along without them. When the simpler methods fail, then I'd proceed to ganglionic blocking agents, but it seems to me that the hazard connected with these compounds is so much more than with the others that I'd put them lower down on the list. This incidentally would go against Dr. Paton's ideas which he elaborated so well regarding the significance of the sympathetic nervous system in the etiology of hypertension. If that were so, I think the availability of these drugs would have answered our problems and made therapeutics very easy and satisfactory. The fact that they have not and that they leave much to be desired would go against the hypothesis that they are correcting what is fundamentally at fault in our hypertensive patient.

DR. DUNSMORE: We have 200 patients on ganglionic blocking therapy and I agree 100 per cent with Dr. Grollman.

DR. DUNCAN: Are there any other thoughts in this direction?

DR. HOOBLER: If you really get the blood pressure down to normal, it is easier to keep it down without blocking agents. It is sometimes good to start with them and then withdraw to simpler therapy, as I think Dr. Freis would do. I am beginning to feel that success breeds success in hypertension, although it is a dangerous thesis to proclaim. Ed, would you want to comment?

DR. FREIS: If you really have had some experience with the ganglionic blocking agents, they're really not so dangerous at all. In fact I think they are pretty safe. I think they're safer than reserpine in big doses over the long pull.

DR. DUNCAN: I hadn't considered these drugs dangerous at all if they are only given to those who have fixed high diastolic pressures, who do not become normotensive under the influence of sedation with Sodium Amytal.

DR FREIS There are a few patients Dr Duncan whom I have treated with blockers who have good responses to Sodium Amytal but whose pressures I haven t been able to control without the use of blocking agents when the patients were ambulatory and working Putting them on a blocker for a short time along with other agents I find, as Dr Hoobler said that this has done something to their hypertension after six months so that I can then do away with the blocker I am unable to select those patients in advance who will do well with a blocker It is just a trial and error business with me Dr Duncan I think that it is a mistake just to consider the possible toxic side effects when you are considering the practice of medicine Of greater importance is the therapeutic benefit derived from the therapy

DR DUNCAN Any other ideas? Dr Moyer?

DR. MOYER I would like to emphasize one point about the use of ganglionic blockers I doubt that there is anything like an unresponsive patient particularly when blockers are used in combination with Rauwolfia and diuretics such as chlorothiazide

DR DUNCAN I would thoroughly agree with that I haven t seen one which you couldn t get down if you gave enough

DR MOYER Then under these circumstances when therapy is indicated I m not completely sold that an Amytal test is necessary

DR DUNCAN It seems to me that it gives me information within three hours which might take several weeks of observation on conservative therapy

DR MOYER This is reminiscent of the time when I first became interested in hypertension and I followed patients along with the Chief of Medicine at our institution He put his patients to bed in the hospital and gave them a grain of phenobarbital every three or four hours and this was supposed to have some kind of therapeutic effect Oftentimes it brought the patients blood pressure down but as soon as they discontinued the phenobarbital and went home they were just as badly off as they were before My point is that it may be better to evaluate such patients as out patients while receiving placebo therapy because I think that the environmental circumstances are relatively important in these patients Putting them in the hospital where the blood pressure may settle down means nothing to me as far as how that patient is going to get along under the circumstances in his home

DR. HOOBLER I ve got to respond to that one because your blood pressures then are those in the office or clinic I want the home blood pressures I think the real way to evaluate a patient s hypertension is not the Amytal test or anything else but what the levels of blood pressure are when taken twice a day for two weeks in the home If they are still very high then I think he carries a risk of hypertensive disease and then I am ready to treat him and record my results on the basis of the home readings

DR MOYER It seems to me that it doesn t matter who takes the blood pressure just so that the blood pressure is taken under circumstances in

which that patient is going to be living not under artificial circumstances such as in the hospital That was the only point I was making When you dwell on patients who get excessively high pressures in the doctors office you are talking about less than 10 per cent of patients

DR. MEILMAN At least if you have this kind of data—home readings I mean—you have something to compare with the office or clinic readings

DR MOYER I might also add that I dont think that it is necessary to admit a patient to the hospital to institute antihypertensive therapy even ganglionic blocking therapy It seems to me that it is much more effective to have this patient under his home environment when adjusting dosages because this is how you are going to have to regulate him sooner or later On an ambulatory basis you can initiate therapy much more slowly You can take a month or two to establish a therapeutic program In that manner you dont get into the problem of over shooting the doses and thus getting into all kinds of side effects When you have the patient at home you can let him take two weeks or more to adjust to a certain dose of the drug Then also you can work out the individual variations in patient requirements because some need a large dose in the morning and others need a large dose in the afternoon and so forth Only when the patient is being studied under the circumstances in which he is going to exist the rest of his life can you really adjust the drug well If the patient has malignant hypertension in which effective reduction in pressure is mandatory immediately what I have just said doesnt hold Im talking about the moderately severe hypertensive in whom therapy is indicated and in whom you have two or three months to develop an effective therapeutic program

DR DUNCAN There are a number of physicians who are interested in this field who dont subscribe to any idea of home blood pressure Is there such a one on the panel so that we could hear the other side?

DR BRUST I think there is a considerable amount to be said on the other side of the story of home blood pressure recordings Most of the patients who come to the doctor to have their blood pressure looked after are trying to find for themselves a physician who assumes the responsibility for their care Dr Freis is going to turn it right back over to him and say "Look its your baby Its your blood pressure You decide how much medicine to take or call me on the phone" It was mentioned earlier today that in terms of home blood pressure recordings it was sometimes important for the blood pressure to be recorded as many as four five or six times a day I think that there are people on this panel who have had experiences with patients on the combined therapy involving the use of blocking agents who once they got the patients taking the blood pressure at home couldnt get them stopped I think there have been some suicidal experiences Im familiar with some of them myself A number of serious psychiatric disturbances have resulted in patients who werent satisfied A hypertensive patient is very frequently a patient who is compulsive and has at least a subclinical type of depression This matter of home blood pressures has to be judged on an individual basis I think thats the important thing I dont think you can use an across the-board rule to apply to all of these people

DR MOYER I would endorse that last statement heartily Not more than 60 to 70 per cent of patients are psychologically suited to having blood pressures taken at home either by themselves or the family

DR MENDLOWITZ I have one comment Dr Duncan that I would like to get across to Dr Paton especially There were a number of comments made in regard to the neurogenic etiology of hypertension and one specifically was the criticism that hypersensitivity to noradrenalin couldn t explain high blood pressure *per se* since the body would then just simply regulate down the amount of noradrenalin secreted I presume this was your idea and therefore the blood pressure would turn out being normal This sort of teleological reasoning under circumstances that are largely unknown has very definite dangers We don t know what makes the body form noradrenalin for the most part We know very little about its local secretion and its titers locally moreover the one clinical condition that we do know a little bit about that is pheochromocytoma runs exactly contrary to this particular thought There you have a high titer of noradrenalin I might say and the body does not lower its own production so as to give normal blood pressure

DR PATON Well I m not adverse to a little teleology but I m sure that if you take a pheochromocytoma and if you swamp the body with noradrenalin no mechanism in the world will overcome it However if you infuse noradrenalin then you can satisfy yourself perfectly well that the body tries to reduce the blood pressure Bradycardia for instance which is so striking after an infusion is perfectly good evidence of it I would have thought that all one has to do is to meditate on the way blood pressure is held tolerably constant to satisfy oneself that the baroreceptors will continue to work in this way I wouldn t care to put any more weight on it than that but I think it s reasonable

DR DUNCAN Any other ideas?

DR MEILMAN I would like to come back to the paper by Dr Ford earlier in the day which pointed out differences in the side effects of Rauwolfia compounds and call to mind several things One the hypotensive dose response curve of Rauwolfia is really quite flat with reference to the hypotensive effect It may not be so flat with reference to the side effects and I wonder whether even though he was able to show similar blood pressure fall by his methods he was really on a different part of the curve with reference to reserpine and alseroxylon that is whether he really did have the minimal effective hypotensive doses of reserpine and alseroxylon to compare the side effects I am not sure in other words that they are really creating different side effects for the same hypotensive effect

DR FORD Did I make it clear that there was no significant difference in toxicity with alseroxylon using dosages from 4 to 32 mg given daily? And that there is a definite difference in toxicity of reserpine between 0 25 and 1 mg?

Part IV

A THE ROLE OF SALT AND DIURETICS IN THE THERAPY OF HYPERTENSION

B SPECIAL PROBLEMS IN THE THERAPY OF HYPERTENSION

A THE ROLE OF SALT AND DIURETICS IN THE THERAPY OF HYPERTENSION

Electrolytes in the Treatment of Hypertension

GEORGE R MENEELY
Vanderbilt University School of Medicine

The late Glen Millikan used to remark that it was time for medicine to move on from the soup to the meat course By this he meant that chemical investigation of the blood and urine had reached the point of diminishing returns while knowledge of abnormalities of the intracellular compartment (if it is a compartment) was just beginning Surely it is true that the liquids" reflect to some extent the cellular chemical architecture but many factors influence the composition of the extracellular domain which are special cellular rather than general Thus the kidney proceeds about its business often without regard for the condition of the cellular territory

The flesh of the body dwells in a state perpetually bordering upon disaster or rebellion Just as the single celled animalcule contends continually with its environment so the cells of the body contend with the *milieu interieur* the "sea within us" for their own survival Just as the single celled animal must wrest from the environment its needed constituents and must push back into the environment its elementary disjecta so the individual cells of the human body must do likewise We marvel at the "constancy" of the internal environment provided for these cells but in fact it fluctuates wildly over the short term compared to the placid chemical composition of its linear ancestor the oceans of the earth Nevertheless the basic problem which confronts the cell of the human body is not much different now than it was in single celled organisms in remote geological antiquity It must extract its needs from its environment and excrete into its environment unwanted excesses and end products of its biochemical activity How it does so is only one determinant of the composition of the extracellular fluid or the plasma part of it and by the same token the plasma level of the various electrolytes is a poor barometer of the weather in the cells The need in medicine now is for more information about cellular electrolyte composition especially of a detailed sort This is manifestly true in the catastrophic electrolyte disturbances of the seriously ill History taking and physical examination may give some partial orientation in electrolyte disturbances but the clinician who believes he can sort out the finer (and sometimes even the coarser) deviations of electrolyte balance as recognizable clinical syndromes is fooling himself and worse sometimes those about him

It is impossible to fly an aircraft without visual reference to a horizontal surface unless it is equipped with instruments which reliably detect the atti

tude and activity of the craft and unless the pilot is qualified correctly to interpret their indications and to act effectively in accord with these indications Even a bird cannot fly if blindfolded and will "spin in just as will the pilot flying blind without instruments or the one ignorant of how to use them We are in a similar predicament in trying to pilot the patient through the turbulent atmosphere of electrolyte disturbances The information we lack is the status of the electrolytes *within* the cells Until we have methods which keep us continually informed of the cellular electrolyte situation we will be engaged in medical seat of the pants" flying while the conditions are really instrument

One of the earliest and still one of the clearest demonstrations of this may be seen from the investigations of Swingle and those working with him[1] After complete adrenalectomy the experimental animal develops a characteristic disturbance of the electrolytes in the circulating blood and soon circulatory collapse supervenes Now if one administers appropriate electrolytes and fluid the plasma electrolyte pattern is restored and circulation is again good Soon once again circulatory collapse occurs but this time the plasma electrolyte pattern remains essentially normal Further administration of fluids and salts is of no avail

If the acute and major electrolyte disturbances are difficult to comprehend and more so to manage how much more completely is information lacking in the chronic and mild deviations! While immediate disaster does not impend evidence indicates that the insidious progress of a number of diseases lies in small but important deviations of intracellular electrolytes away from the normal or optimal condition One of these states seems to be hypertension

In order to discuss electrolytes in hypertension it is necessary to consider some of the recent revisions of our understanding of the manner in which electrolytes exist in cells and how they move into and out of this domain This topic has recently been reviewed by us Present evidence indicates that there is a water space within cells which is identical in cation and anion composition with the surrounding medium It further appears that ions can enter or leave this space at very rapid rates Beyond this "water space" and here the word beyond" indicates sequentially rather than spatially the ions exist in an "ion exchange or electron sharing relationship with organic constituents of the cells This organization seems to be quasi crystalline in nature and the relationship of the electrolytes to the organic constituents is an intricate matter of interatomic energetics A system of energy levels must be believed to exist comparable to but infinitely more complex than in a semi conductor "transistor It has long been evident that the transfers of energy which occur in the living cell come down in the end to transfers of electrons and doubtless just as in man made semiconductor devices the transfer of holes as well Since a "hole" is a place where an electron could be but is not it is seen that the transferring of holes" is more in the manner of a notation than any real concept of the presence of units of positive electricity Nearly fifty years ago as Griffith[3] has pointed out it was necessary for F Gowland Hopkins to urge organic chemists not to turn away from the presumed hopeless complexity of intracellular metabolic chemical reactions Now the time has come for us to exhort the solid state physicists to come to the aid of the biologists and break open what has seemed this "forbidden band" but what really is only an area of ignorance

The relationship between the ions of the cellular water space and those associated with the molecular constituents of the cells is principally dependent upon the configurative receptiveness of the molecular constituents and only partly upon the influences of statistical pressures The exchangeable ions have to be considered as loosely or tightly bound in varying degrees depending upon the general and the momentary special opportunities for electron sharing with the various organic molecules The older concept that the intracellular electrolytes simply made up an intracellular "medium much as the extracellular ones make up the *milieu interieur* is evidently quite wrong and misleading in serious ways To be sure intracellular electrolyte composition can be influenced by mass action effects of increases or decreases in the relative abundance of one or another ion in the surrounding medium and evidently it is not at all difficult to distort the condition of the surrounding medium to such an extent that the cell can no longer live successfully within it Still in real life these are usually second order effects The cell has a powerful ability to glean from its environment what it may need including electrolytes and to reject what it does not want This is the property of the cell which deceives us when we lightly dismiss the importance of moderate changes in the cellular environment as possibly deleterious in the long term for the organism as a whole Any physiologic displacement must be compensated by some other displacement elsewhere in cellular economy It has been shown that yeasts may be made to operate with sodium as the principal intracellular electrolyte[4] but there is no evidence that the yeast cell is pleased with the situation and the extent to which its activity under these circumstances is disadvantageous is entirely unknown

✓There is a growing body of evidence (see previous reviews and the report of Dahl elsewhere in this volume) that excessive intake of sodium chloride may be a potent factor in the genesis of human hypertension and there is evidence[5] that an increased potassium intake may have a protective effect against some (but not all) of the adverse effects of increased sodium chloride ingestion In my earlier paper in this volume I discussed what may be the explanation of why our understanding of the roles of sodium and of potassium in hypertension is inchoate It is clearly evident that human consumption *of sodium chloride is greatly in excess of real need for it* Whether this unnecessarily high salt consumption of all civilized peoples of the modern world is really harmful has so far not been flatly proved but the evidence both circumstantial and direct is indeed strong There is some evidence that we may be reducing our potassium intake at the very time we *increase our need for it by our excessive use of sodium chloride*

For practical purposes and within present knowledge sodium and potassium are the electrolytes of interest in hypertension Ambard and Beaujard[1] were the earliest (1904) to advocate salt restriction in hypertension but the emphasis was on the chloride In 1914 Macht[7] showed that sodium was constrictor and potassium dilator for small arteries Allen and Sherrill in 1922 presented their well known work on salt restriction in hypertension In 1928 Addison[8] produced a fall in blood pressure by administration of various salts of potassium to patients already on a low sodium diet Priddle[9] reinforced these findings in 1931 McQuarrie[10] made interesting observations of the effectiveness of potassium salts in lowering blood pressure not only during sodium chloride restriction but also when sodium chloride was being consumed at high levels The Kempner rice fruit diet[11] is not only a low

tude and activity of the craft and unless the pilot is qualified correctly to interpret their indications and to act effectively in accord with these indications Even a bird cannot fly if blindfolded and will "spin in" just as will the pilot flying blind without instruments or the one ignorant of how to use them We are in a similar predicament in trying to pilot the patient through the turbulent atmosphere of electrolyte disturbances The information we lack is the status of the electrolytes *within* the cells Until we have methods which keep us continually informed of the cellular electrolyte situation we will be engaged in medical seat of the pants" flying while the conditions are really instrument"

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several male former associates have shown an intent to proceed with the recommendations of the lines which follow those above

One may conclude that there is little doubt that excess salt has an important role in human hypertension and the animal evidence of the merit of extra potassium in protecting against toxic effects of excessive sodium intake is clear The question should be raised whether we ought not embark upon a major investigation of the well being of humans as influenced by sodium and potassium intake Much work is going on in this area now and much more needs to be done Present evidence indicates that the foundation of therapy (and prophylaxis) in hypertension should be restriction of sodium chloride intake or its enhanced excretion by artificial means while at the same time assuring a plentiful intake of potassium

As earlier stated it is not now possible correctly to manage electrolytes in the therapy of hypertension because we lack instrumental methods suitable for routine use in determining total body sodium and potassium Cumbersome radioisotope methods are available for research purposes and should be used more frequently Aside from this what can we do that is practical? First let us mention one thing which will *not* work In normal individuals 24 hour chloride excretion closely parallels sodium excretion This is *not* true in disease states and should not be trusted"[1]

The basic aim stated above of sodium restriction or depletion when total body sodium is excessive while assuring a sufficient supply (but not too much) potassium can be approximated by following plasma sodium and potassium levels and the 24 hour urine excretions of both The situation in severe renal failure is extremely tricky and aside from this word of caution is not discussed here In patients whose renal function is not too seriously impaired the plasma sodium level perhaps most accurately reflects the status of sodium in the body If control of total sodium is accomplished by dietary restriction or by resins the amount in the urine accurately reflects the degree of control of what actually enters the body but if diuretics is the control method the intake too must be known which is well nigh impossible away from a metabolism ward Some extra potassium must come through in the urine perhaps 20 to 30 milliequivalents per day else the patient will develop symptoms of potassium privation[13] If the kidney is incapable of excreting potassium it can be an efficient poison This difficulty can be forfended by close watch over plasma levels and the electrocardiogram

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Low-salt Diet in the Treatment of Hypertension

ARTHUR GROLLMAN

University of Texas Southwestern Medical School

The restriction of the dietary intake of sodium chloride in the therapeutic management of patients with hypertension has been advocated periodically throughout the present century Ambard and Beaujard[1] in 1905 recommended the exclusion of salt from the diet of hypertensives Allen and Sherrill in 1922 advocated the treatment of arterial hypertension by salt restriction a procedure which was adopted and widely used in Europe but

which received relatively little attention in this country Most of the earlier observers believed that the beneficent effects of a salt poor diet were ascribable mainly to chloride restriction they had little appreciation of the significance of the sodium ion in salt restriction Moreover since little was known of the role of sodium in body metabolism there was no rationale for the procedure and most competent clinicians did not consider it worth while Although many patients were often instructed to avoid salty foods and not to add any excessive quantity of salt to their food there was no objection to its use in sufficient amounts to render it palatable Since as is now well known moderate restriction of sodium fails to influence the blood pressure it is evident why this form of therapy proved unsuccessful Moreover the fact that the addition of moderate amounts of salt to a normal diet caused no increase in blood pressure either in the normal or hypertensive patient or in the experimental animal[3] militated against the acceptance of this form of therapy as worthy of the trouble necessary for carrying it out

The dietary management of hypertension received a new impetus following the demonstration of the effectiveness of a rice diet by Kempner in 1944 This author attributed the effects of this diet to such factors as its low protein content and to hypothetical enzymatic effects He did not consider its low salt content as contributing to its effectiveness In an investigation of the effects of various diets on the blood pressure and survival of hypertensive rats Grollman and Harrison[4] demonstrated the capacity of drastic sodium restriction to lower the blood pressure in such animals and to prolong their survival They demonstrated that this effect of a monotonous diet was not limited to rice but could be obtained by other salt free foods or simply by the restriction of sodium They showed moreover that the addition of sodium salts to rice or other monotonous diets prevented the hypotensive action of such diets These authors and their colleagues then applied the procedure to patients and confirmed the previous results on animals By the use of dialyzed milk and other foods low in sodium content it was possible to prepare nutritionally adequate diets Of six hypertensive patients marked reduction in blood pressure occurred in two a moderate reduction in three and there was no appreciable effect on the sixth subject[6]

During the subsequent decade little attention was paid to the use of sodium restriction in the treatment of hypertension However the recognition of the importance of electrolyte and water metabolism in the animal economy of the role of the adrenals in regulating this metabolic function and the effects of electrolytes and the adrenal on blood pressure renewed interest in the field and a rationale for sodium restriction became evident It is now established that restriction of sodium is a definitely useful procedure in the hypertensive which under most circumstances is attended by no serious side effects The effectiveness of diuretics as hypotensive agents as shown later is probably dependent upon their natriuretic action

The mechanism whereby drastic sodium restriction reduces the blood pressure of some patients is still not established with certainty Because of the importance of the sodium ion in the electrolyte water balance of the cells and body fluids it is probable that sodium restriction acts by its effects on the fluid compartments of the body In patients as well as in experimentally induced hypertension an expansion of the volume of the extracellular fluid[7] and an increase in the total water[8] have been demonstrated

It is unlikely that sodium restriction in lowering the blood pressure funda

mentally affects the basic defect responsible for hypertension It represents more likely an indirect empirical procedure which through its effects on the fluid compartment of the body exerts a nonspecific lowering of the blood pressure

The importance of sodium restriction in the management of the hypertensive patient has assumed new importance with the introduction of non toxic natriuretic agents By the use of such diuretics (chlorothiazide [Diuril]) in association with moderate sodium restriction the goals of drastic sodium restriction may be obtained without difficulty

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The Effect of a High Salt Intake on the Treatment of Hypertension

MARVIN MOSER
Montefiore Hospital New York City

A relationship between the occurrence of elevated blood pressure and a high salt intake has been suggested repeatedly in both human and animal experiments[1 4] It has been demonstrated in the experimental animal by Meneely[3] Sapirstein *et al*[4] Rodbard and others that a high salt intake with or without the use of a sodium retaining hormone such as DOCA will produce a hypertensive state similar in most respects to human hypertension This apparent correlation between blood pressure elevation and salt intake has more recently been stressed by the continuing studies of Dahl and Love in humans[6] Reports from the Orient[7] and the West Indies[8] also suggest that in areas of high salt intake the prevalence of elevated blood pressure is high although factors other than salt intake have not been eliminated as reasons for the apparent frequency of hypertension

Little doubt remains on the other hand that restriction of sodium intake will lower the blood pressure in many hypertensive subjects and that the effectiveness of the "rice diet in treatment is solely dependent upon sodium restriction and not upon restriction of protein or other food elements[9 10] The degree of sodium restriction necessary to produce and maintain a fall in blood pressure when utilized as the *sole* method of treatment has also

been clearly defined Watkin and coworkers[9] and Hatch[10] have demonstrated that diets containing more than 300 to 500 mg of sodium daily are generally ineffective in the treatment of hypertension and that the addition of 1 0 to 3 0 gm of sodium chloride to the rice diet which contains less than 200 mg of sodium prevented the expected fall in blood pressure If salt is added *after* a suitable period on drastic sodium restriction a definite rise in blood pressure results (Figs 1 and 2) The degree of sodium restriction therefore would appear to be critical when hypertensive patients are treated with diet *alone*

In an effort to clarify further the role of sodium in the treatment of hypertension Stead *et al*[11] determined that the blood pressure fall following the use of a short acting ganglion blocking agent tetraethylammonium chloride was more pronounced after marked restriction of salt in some patients Other hypertensives however showed no difference in either random blood

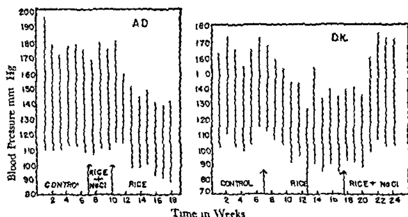


Fig 1 Case A D Failure of blood pressure to fall when without knowledge of patient 3 0 gm NaCl daily was added in capsule form at the start of the rice diet blood pressure fell rapidly when salt was withdrawn Case D K Addition of 1 0 gm NaCl daily in capsule form to otherwise unmodified rice diet caused early return of blood pressure toward control levels after good response to rice diet had been obtained (From Watkin D M et al Am J Med 9 441 1950)

pressures or pressures after TEAC during "desalted" or "salted" periods (Figs 3 and 4) Conclusions cannot be drawn from these data regarding the degree of salt restriction if any necessary to produce a maximum blood pressure lowering effect in hypertensive patients treated with ganglion blocking agents although it would appear that in certain patients salt restriction was additive

Blood pressure lowering following surgical sympathectomy is enhanced by salt restriction in many instances Restriction usually need not be as rigid as when diet is the only therapy Similarly in some cases being treated over a long period of time with the ganglion blocking drugs hydralazine and/or reserpine drug effect appears to be aided by even moderate salt restriction[12] The critical" level of salt intake above which drug effect will be nullified has not as yet been clearly defined

With the introduction of chlorothiazide in the therapy of hypertension an opportunity to produce adequate continuous salt "depletion" without

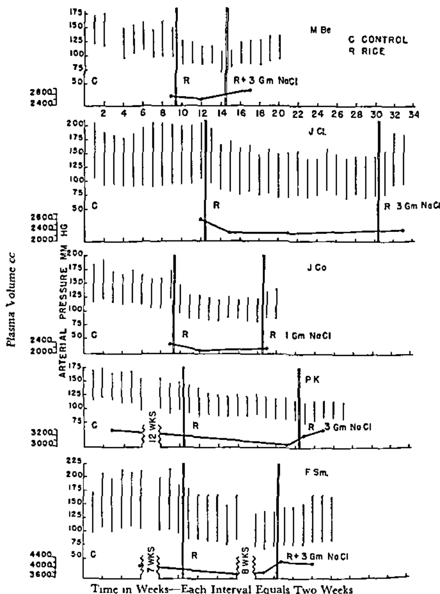


Fig 2 Changes in arterial pressure and plasma volume (T 1824 space) in five patients with essential hypertension on strict rice diet and following addition of 1 or 3 gm of sodium chloride daily The top of each vertical bar indicates mean basal systolic pressure for one week and bottom of bar the corresponding diastolic pressure The heavy line below indicates concomitant plasma volume changes (From Watkin D M *et al* Am J Med 9 441 1950

drastic dietary restriction presented itself Numerous observers have confirmed the fact that the production of salt loss by this agent enhances the antihypertensive effect of the other drugs presently utilized in the treatment of hypertension [13, 14, 15] That this enhancement is secondary to the effect of chlorothiazide on sodium metabolism and not upon some other factor or factors is almost universally agreed upon Freis [13] Wilkins [14] and others have also demonstrated that the progressive addition of sodium chloride to

Fig. 3 Mean random pressures and TEAC floors by periods for each patient of group I (From Stead W. W. et al J Clin Invest 27 766 1948)

the diet will eliminate or decrease the chlorothiazide effect on blood pressure to a great extent

Recent rigidly controlled placebo-chlorothiazide studies over a period of five months in the Bahamas on a group of 42 hypertensive patients with a high salt intake (12 to 27 gms NaCl daily) demonstrated that only three

Fig. 4 Comparison of the means of random pressures and TEAC floors in control (salted) and desalted periods for the patients of group II (From Stead W. W. et al J Clin Invest 27 766 1948)

individuals maintained a fall of diastolic blood pressure in excess of 10 mm of mercury on 1 5 gm of chlorothiazide daily as the only therapy Four patients experienced a fall of 20 mm or more in systolic pressure These observations further suggest that a high salt intake may prevent the blood pressure response to chlorothiazide and are in contrast to observations on patients maintained on diets containing smaller amounts of sodium where some sustained blood pressure reduction is usually noted following the use of this drug

Few studies have been performed that have actually demonstrated a level of sodium intake in hypertensive patients who have responded to combination drug therapy above which the drug effect is partially or completely eliminated Suggestions that this is in fact the case have been repeatedly made but few confirmatory data on salt loading in these patients are available Since practically all hypertensive patients are immediately placed on some level of salt restriction as a major part of therapy it may be of some importance to define the levels of intake that will provide an adequate palatable diet and yet not reduce the effectiveness of other forms of treatment. Observations on a small group of ambulatory hypertensive patients who had obtained excellent blood pressure responses to combination drug therapy may be of interest in this regard These data are preliminary and in the nature of a pilot study to suggest leads for further more definitive investigations

The patients reported upon were out patients who were recording their pressures at home four times daily and had been stabilized for periods of from two to nine months on specific antihypertensive drug therapy before salt loading was attempted In two of the cases here cited daily 24 hour sodium excretions were obtained for the duration of the study to date In the others 24 hour sodium excretions were determined as frequently as feasible Creatinine excretion served as a check of the validity of the 24 hour output All of the patients were advised to remain on their usual diets and salt intakes and continued their usual activity They were informed that the study was to determine whether or not they required *more* or *less* salt in their diets so that a conscious effort on the part of the patients to limit or increase salt intake would not be made No attempt was made to fix the salt content of the diet and daily fluctuations in intake were expected After several months of blood pressure control and after an additional three week period during which sodium excretion was measured 6 gm of sodium chloride were added to the diet in the form of noncoated tablets Other medication was continued without change throughout the entire period

Observations based on data collected to date on five patients suggest that adequate blood pressure lowering can be achieved when ganglion blockers and chlorothiazide are given in combination despite a relatively high normal sodium intake (8 to 12 gm NaCl daily) Increases in sodium intake above 15 gm daily appear to result in a slight rise in blood pressure (especially systolic) approximately five to ten days following the increase in salt intake (Blood pressure rise correlated in some instances with a slight but definite increase in weight) It appears that blood pressure elevation occurs sooner after salt loading and is more dramatic if the previous antihypertensive effect of drugs had been obtained in conjunction with a low or moderately low sodium intake (under 5 to 6 gm) An illustration of this effect is noted in Fig 5 which summarizes data on a 32 year old colored female who

had been successfully treated with a combination of mecamylamine (20 mg/day) chlorothiazide (1 gm/day) and reserpine (.5 mg/day) and had been told in the past to limit her salt intake Excretion studies revealed a sodium output slightly under the average of persons on a "normal" diet (average 113 mEq Na/day) When 6 gm of extra sodium chloride were added to her diet a slight but apparently sustained rise in both diastolic and systolic blood pressure occurred Average "preloading" blood pressure was 139/92 after salt addition 151/100 mm Hg Observations are continuing and it is planned to increase sodium intake still further

These tentative observations tend to confirm previous clinical impressions but obviously no conclusions can be drawn from them They suggest however that there may be a level of sodium intake above which drug effect on blood pressure lowering may be inhibited but that rigid restriction of sodium is probably not necessary to produce an adequate blood pressure fall when potent antihypertensive drugs are used especially when chlorothiazide is employed Further long term carefully controlled studies are necessary to clarify this problem

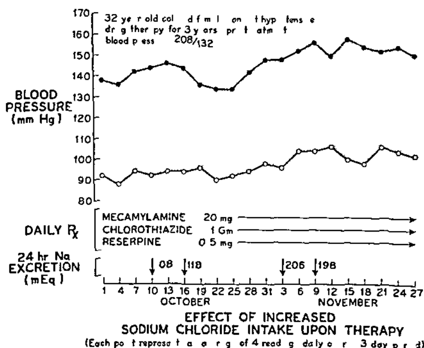


Fig 5 An increase in salt intake from approximately 6 gm to 12 gm daily appeared to produce a slight but definite rise in blood pressure in this patient despite continuation of antihypertensive drug therapy

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Discussion

Calvin Kay *Moderator*	Arthur Grollman
John Beem	Carroll Handley
Karl Beyer	William Hollander
William Daeschner	Sibley Hoobler
Harriet Dustan	George Meneely
Ralph Ford	Lewis Mills
Edward Freis	Marvin Moser
Robert Gaunt	William Paton
Ray Gifford	Bertram Winer

Dr Kay Later this morning after we have heard from Drs Handley Freis and Grollman we should be able to make a number of generalizations about the role of salt and diuretics in the therapy of hypertension It is apparent that sodium plays a very important role Sodium restriction or saluresis reduces blood pressure We will consider the possibility that sodium imbalance may be the basic etiology of hypertension or that it may increase

the severity chronicity and irreversibility of hypertension Is it not also true that hypertension promotes hypertension as we have come to believe that heart failure begets failure? Do you think it is possible Dr Hoobler that sodium is the fundamental factor and that we may not have to consider pressor substances?

Dr Hoobler I speculate that there is a fundamental maldistribution of sodium that may be the ultimate cause of vasoconstriction creating the hypertension however this maldistribution of sodium within and without the cell might be mediated by angiotensin desoxycorticosterone or unknown pressor substances I doubt that excessive salt ingestion creates hypertension because experimental sodium feeding does not cause hypertension in a human being even when he is genetically predisposed and secondly because epidemiologic data do not support the thesis These statements can be challenged and it is easy to find apparent correlations and to overlook discrepancies For example in the Bahamas Dr Moser and I this year found areas where the incidence of hypertension was twice that of other areas with about the same salt intake in each group of people Once we get good epidemiologic studies throughout the world I am sure we will find the incidence of hypertension is not greatly altered by the salt intake

Dr Kay Dr Grollman might sodium alone or jointly with some endocrine abnormality be the basis for the altered vascular reactivity? Fundamentally then could it be that there is no pressor substance?

Dr Grollman I believe the latter is definitely possible I think only rarely is a pressor substance involved The deviation in electrolyte and water metabolism which we observe in the hypertensive merely reflects one of the changes of a systemic disease Similar deviations occur in many disorders In contrast to what Dr Hoobler has said I think it is quite conceivable in some individuals that there may be a correlation between hypertension and the intake of large amounts of salt In certain areas of the world such as Java where the intake of salt apparently amounts to 50 or 60 gm daily hypertension may be more prevalent Such salt intake is comparable to that which Dr Meneely has shown will induce hypertension in the rat Indeed a lesser intake of perhaps 30 gm which is not at all uncommon in our own population might precipitate the development of hypertension at 30 or 40 years of age in a genetically predisposed individual whereas such an individual on a diet containing only 5 gm a day might not develop the disease However I do not think essential hypertension would disappear if we all gave up the salt shaker

The adrenals are active in salt and water metabolism Experimental removal of one kidney and the administration of adrenal extract and salt results in hypertension Each of these three factors may elevate blood pressure and the combination certainly does so

Dr Meneely I disagree with Dr Moser s statement that the sole effect of the rice fruit diet is the diminished sodium The diet also has a very high potassium content. Increased sodium ingestion does produce hypertension in the rat and I think the burden of proof is to show that it does not in people The amount of salt which we have fed rats might appear very high

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Discussion

CALVIN KAY *Moderator*	ARTHUR GROLLMAN
JOHN BEEM	CARROLL HANDLEY
KARL BEYER	WILLIAM HOLLANDER
WILLIAM DAESCHNER	SIBLEY HOOBLER
HARRIET DUSTAN	GEORGE MENEELY
RALPH FORD	LEWIS MILLS
EDWARD FREIS	MARVIN MOSER
ROBERT GAUNT	WILLIAM PATON
RAY GIFFORD	BERTRAM WINER

DR KAY Later this morning after we have heard from Drs Handley Freis and Grollman we should be able to make a number of generalizations about the role of salt and diuretics in the therapy of hypertension It is apparent that sodium plays a very important role Sodium restriction or saluresis reduces blood pressure We will consider the possibility that sodium imbalance may be the basic etiology of hypertension or that it may increase

DR WINER In contrast to the study by Holly and another paper published in *Circulation* this past year my patients were all uncomplicated hyperten sives none had congestive failure and none had malignant hypertension In uncomplicated hypertension in my series the serum sodium was equal in the two groups

DR HOLLANDER Direct balance studies indicate that as the sodium con tent of the diet is increased there is a retention of sodium and body sodium does indeed increase

DR KAY Let us return to another subject that was mentioned briefly by two of our speakers this morning namely the handling of sodium in patients who have hypertension and serious renal disease perhaps associated with retinal hemorrhages and exudates convulsive seizures edema and uremia We all recognize that some of these patients respond badly to restriction of sodium On the other hand sodium restriction should be useful for some of these abnormalities Yet in the presence of uremia we have twice this morn ing been cautioned to be extremely careful I submit that in most of these cases we are too careful about restricting sodium we should restrict it even further than is done The hazard has been overemphasized in edematous or significantly hypertensive patients

DR GROLLMAN I agree that this hazard has been greatly exaggerated However certain renal disturbances in which the kidney is unable to con serve sodium may result in a loss of extracellular fluid volume when sodium restriction or diuretic therapy is attempted Thereupon further failure of the circulation decreases renal blood flow and progressive uremia causes death This hazard does exist but only under obvious conditions which we recognize clinically The results of injudicious use of sodium restriction or diuretics may be corrected by the administration of hypertonic saline solution

DR KAY Assume that this patient also has a metabolic acidosis in which one would like to give sodium except for the presence of severe hypertensive disease Dr Dustan

DR DUSTAN This problem does occur rather frequently First I would like to emphasize your remark that many patients with primary renal dis ease uremia and secondary hypertension should have their sodium intake restricted Accelerated vascular disease associated with primary renal disease responds very well to sodium restriction Although perhaps there is some risk of sodium depletion such therapy should not be denied these patients The danger signs are obvious if you look for them A basic low sodium diet is valuable and this usually means protein restriction in addition Bicarbo- nate may be added if necessary

DR KAY When patients have major hypertensive disease associated with renal disease sodium restriction and chlorothiazide are often very helpful Subsequently when blood pressure falls and acidosis remains I have found it clinically useful to give these patients sodium bicarbonate and chlorothia zide This therapy seems to have a beneficial chloruretic effect and acidosis is diminished

DR MOSER What do the panelists think about the effect of chlorothiazide and sodium restriction upon potassium balance in a patient with severe renal disease? The only difficulty we have had with such patients resulted from hypokalemia

DR FREIS It is my impression that uremia or increasing azotemia in these patients results primarily from the reduction of blood pressure rather than from any serious electrolyte depletion except in salt losing disorders Serum electrolytes should be determined but these patients should not be denied antihypertensive therapy

DR HOOBLER We must remember that in the presence of oliguria or anuria sodium administration can produce hypertension and hyperkalemia may cause death

DR KAY The magnitude of the urinary output of course is tremendously important Although patients with a large urinary output may develop serious electrolyte imbalance they are rarely troubled with potassium retention Quite the contrary when the urinary excretion is low one must be very careful about hyperkalemia

DR. MENEELY Amplifying my earlier answer I think determination of plasma sodium is an inadequate measure used in desperation Measuring the twenty four hour urine excretion of sodium is much better

DR KAY Which determination is the most expensive?

DR MENEELY The chemical determinations are virtually the same The house physician collects the blood specimen whereas a technician or nurse collects the urine specimen

DR HOLLANDER Unless the sodium intake is known the twenty four hour urine sodium means little or nothing

DR. MENEELY It is very helpful if you are trying to restrict someone's sodium and they have 5 or 6 gm of sodium chloride in their urine every day

DR KAY Then you are using this as a policing procedure

DR DAESCHNER An interesting corollary may be drawn from children concerning the relation of salt to hypertension In childhood hypertensive disease is extremely rare frequently complicated and almost always associated with either a transient or prolonged decrease in renal function and reduced ability to excrete salt

DR KAY Assume that a specific patient on a restricted salt intake excretes an additional 300 milliequivalents of sodium in a twenty four hour period as a result of chlorothiazide therapy Thereafter assume the sodium intake and output remain at approximate equilibrium When would one expect the maximum effect upon blood pressure—in a few hours or in several days?

DR HOOBLER In the presence of sympathetic nervous system inhibition the response of the blood pressure to saluresis roughly parallels the weight

loss Otherwise the blood pressure response is variable sometime paralleling the initial weight loss sometimes independent of weight loss perhaps occurring days weeks or months after continued therapy with chlorothiazide

DR KAY Therefore if a patient lost twelve pounds in three days on such a program and the blood pressure had not fallen a millimeter of mercury it would not necessarily mean that this patient would never respond if the program was continued for several additional weeks

DR. FREIS I must disagree with that. There are two types of response In one the blood pressure does not fall as a result of chlorothiazide therapy although you do get a depletion of salt In the other the blood pressure does fall in association with the diuresis and saluresis which may be complete in perhaps forty eight hours after institution of chlorothiazide therapy whereupon the maximal blood pressure reduction has occurred

DR HOLLANDER I agree with Dr Freis Balance studies indicate that the *antihypertensive effect of chlorothiazide occurs within twenty four hours* after the administration of the compound and in association with a marked reduction in the body sodium However if chlorothiazide is given in combination with Rauwolfia or hydralazine the maximal blood pressure reduc*tion may not be attained for one to three weeks*

DR KAY In other words these other preparations might be ineffective in the absence of an environment of restricted sodium and even then they manifest their usual delayed onset of action when administered orally

DR FREIS The blood pressure response to chlorothiazide is most prompt in the sympathectomized patient and in the patient who is receiving ganglion blocking agents apparently because the moderator reflexes are blocked

DR WINER Chlorothiazide may increase other effects of ganglion blockade such as postural hypotension dryness of the mouth constipation et cetera This may be related to an effect on renal excretion of the drug or perhaps upon gastrointestinal absorption It is as though more blocking drug were given.

DR BEEM In our experience when chlorothiazide is administered with a ganglionic blocking agent the augmentation of vasodepressor response far exceeds any influence on side effects such as result from blockade of the parasympathetic nervous system The efficacy of such combination therapy of course necessitates relatively small doses of ganglionic blocking agents and indeed this usually results in a better tolerated regimen than has been possible heretofore

As predicted the elevation of urine pH associated with chlorothiazide therapy somewhat diminishes the renal elimination of mecamylamine However it is doubtful that this is the major mechanism of antihypertensive action of chlorothiazide since it is effective in surgically sympathectomized patients It augments the vasodepressor response to other ganglionic blockers the excretion of which is not known to be dependent on urine pH and it augments the response to nonganglionic blocking vasodepressors—not to mention its antihypertensive action in the absence of other vasodepressor agents in certain patients

Pharmacology of Mercurial Diuretics and Chlorothiazide

CARROLL A HANDLEY

Baylor University College of Medicine

With the advent of safe and effective agents over the past two decades diuretics have become much more extensively employed This is particularly true since the introduction of effective oral diuretics At one time these agents were used chiefly to treat patients with congestive heart failure and edema due to cirrhosis Currently they are employed successfully for controlling a number of different edematous states and as an adjunct in the treatment of hypertension These edematous states include premenstrual edema edema of pregnancy hepatic disease nephrotic syndrome and "steroid" edema While the causes of edema in these various states may differ fundamentally they all have one factor in common and that is salt and fluid retention

The exact mechanism or mechanisms causing a retention of salt and water in heart failure are still in doubt although considerable effort has been and still is directed toward the solution of this problem As the dominant ion of the extracellular fluid sodium and its associated anions assume great importance in the regulation of body fluid An increase in renal tubular reabsorption of as little as 1 per cent of filtered sodium per day would mean the gain of about 11 grams This would result in the retention of more than three liters of water to maintain the normal osmolarity of the extracellular fluid.

Several factors should be considered in choosing a diuretic including possible untoward reactions relative potency tendency for drug tolerance and the electrolyte pattern produced While a number of diuretics may be equally effective for controlling the several types of edema it may be wise to exclude the use of some of them in certain edematous states because of their pharmacologic properties

The following discussion will be arbitrarily restricted to two types of diuretics organomercurials and chlorothiazide

ORGANOMERCURIAL DIURETICS

The mercurial diuretics are the most potent duretic agents discovered The most commonly used parenteral mercurial diuretics are meralluride (Mercuhydrin) mercaptomerin (Thiomerin) merethoxylline (Dicurin) mercurophylline (Mercuzanthin or Mercupurin) and mersalyl (Salyrgan) Chlormerodrin (Neohydrin) is the most commonly used oral mercurial

As early as 1928 Govaerts[1] provided unequivocal evidence that diuresis from a mercurial diuretic could be produced by a direct effect on the kidney He administered an organomercurial diuretic to a dog and at the time of maximal diuresis transplanted a kidney to a recipient dog The donor kidney

continued to diurese while the recipient animals kidneys continued to secrete urine at the control rate Additional evidence of the same nature was obtained by injecting a small amount of a mercurial diuretic into one renal artery of a dog The injected kidney showed diuresis but the urine output of the other side remained constant In this experiment the injected kidney retained most of the diuretic

Electrolyte and Water Excretion Undoubtedly the most important therapeutic effect of the mercurial diuretics is a partial inhibition of the rate

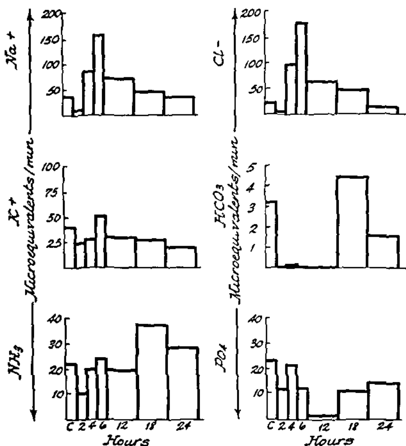
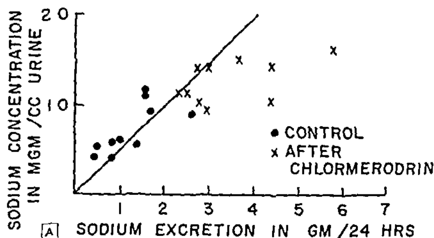


Fig 1 Patterns of electrolyte excretion following the intramuscular administration of 1 cc of meralluride to a cardiac patient

of sodium and chloride reabsorption by the renal tubules It is generally assumed that specific transport systems are present in the cells of the renal tubule for the reabsorption and secretion of different ions and compounds present in the glomerular filtrate and the blood The composition of the urine before and during mercurial diuresis indicates a highly selective action on only a few of these transport mechanisms Among the urinary electrolytes the reabsorption of sodium and chloride is blocked to the greatest extent There are proponents of the view that the primary effect is on chloride re absorption others favor a primary effect on sodium While it is true that

there is frequently a greater relative increase in the rate of chloride excretion this may indicate an increased rate of excretion of cations other than sodium

The effect of mercurial diuresis on potassium excretion is variable It is either increased decreased or is not changed Mercurials depress the renal



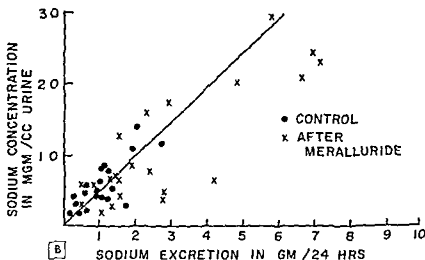


Fig 2 A Increased sodium excretion as well as increased concentration of sodium per cc of urine after intramuscular administration of 40 mg of Hg equivalent of chlormerodrin (Neohydrin)

B Similar effects from the same dose of meralluride (Mercurhydrin)

tubular secretory mechanism for potassium [3] No serious disturbance of potassium metabolism occurs in the usual clinical use of these agents However if ammonium chloride is used concomitantly with a mercurial or if dietary sodium is retained during diuretic therapy the loss of potassium may be appreciable This may account for such symptoms as muscular weakness nausea and ventricular premature contractions

Calcium excretion may be moderately increased by mercurials The ex

cretion of phosphate sulfate ammonia hydrogen ions or titratable acidity are not influenced during the period of maximal diuresis and natriuresis The mercurials do not produce a predictable effect on urinary pH

During mercurial diuresis a greater increase in the rate of excretion of sodium chloride than of water usually occurs This is reflected in an increase in concentration of sodium per unit volume of urine formed In contrast to

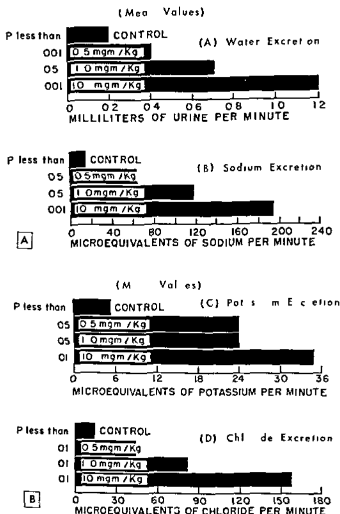


Fig 3 A Urine volume and sodium excretion after several different intravenous doses of chlorothiazide in dogs

B Potassium and chloride excretion in the same dogs observed in A

the action of these diuretics when cardiac failure is controlled with digitalis alone sodium and chloride are lost in the urine in the same concentration as they are present in the extracellular fluid [4 5]

No specific effect of mercurial diuretics on tubular reabsorption of water has been demonstrated Increased rates of sodium and chloride excretion usually but not always precede water diuresis [6] The rate of excretion of

these two ions increases five or sixfold in the average cardiac patient whereas urine volume may only increase two or threefold[7]

The sodium chloride and water loss during mercurial diuresis can be accounted for as originating entirely from the extracellular fluid The fall in plasma potassium however is by no means great enough to account for the potassium loss as coming from extracellular fluid alone Actually the potassium loss during diuresis is sometimes greater than the total calculated

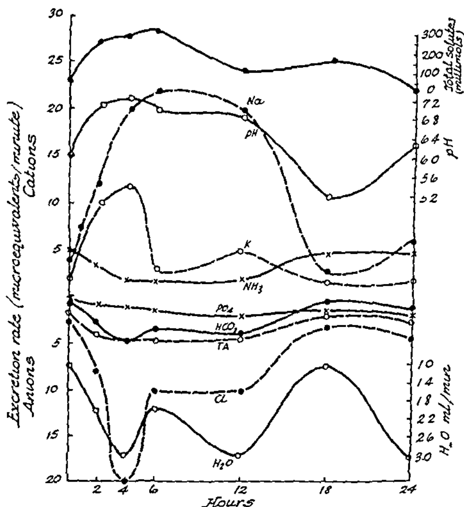


Fig 4 Typical electrolyte excretion patterns after oral administration of a single 2000 mg dose of chlorothiazide

amount of extracellular potassium Intracellular loss of potassium undoubtedly occurs

The increased rate of excretion of salt and water begins *within two hours* after administration and persists for 12 to 18 hours

Toxicity There has been some hesitancy in the past to use mercurial diuretics for fear they might release inorganic mercury and produce symptoms of mercury poisoning These fears were unfounded as can be attested by the absence of toxic symptoms in patients receiving these compounds for

a number of years Also recent studies of the excretory products from mercurials indicate they are largely excreted in an unmodified form [8, 9]

CHLOROTHIAZIDE

The recent introduction of *chlorothiazide (Diuril) a potent orally active* agent has enlarged the scope of diuretic therapy This agent a nonmercurial heterocyclic acid offers the advantage of being just as effective orally as parenterally

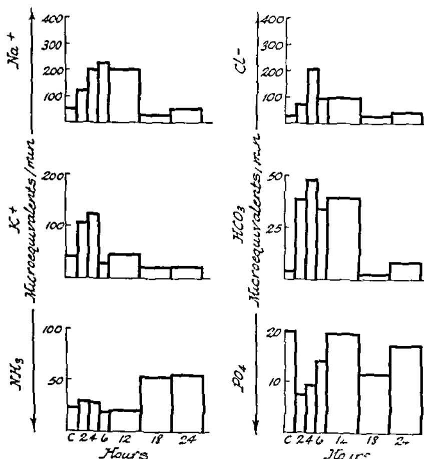


Fig 5 Patterns of excretion following administration of chlorothiazide 2000 mg orally

Mechanism of Action Chlorothiazide is an effective inhibitor of carbonic anhydrase *in vitro* This does not appear to be the primary mechanism for producing diuresis however with effective diuretic doses the increased rate of sodium excretion is nearly balanced by increased chloride excretion There is a moderate increase in the rate of potassium and bicarbonate excretion *and little change in urinary pH* [10, 11] *The urinary electrolyte pattern* is more characteristic of that seen during mercurial diuresis than that associated with carbonic anhydrase inhibition

Following the administration of chlorothiazide water excretion seems to

be a secondary phenomenon since not only the absolute excretion of sodium and chloride increases but the concentration of these electrolytes in the urine increases also The greatest responses are seen during the second two hour period following the oral administration of the drug (Fig 4) with persistence of the response at a lower level for 12 hours and return to control levels during the third six hour period (18 hours after the drug)

As the dose of chlorothiazide is increased the electrolyte excretion pattern becomes more characteristic of that observed with carbonic anhydrase

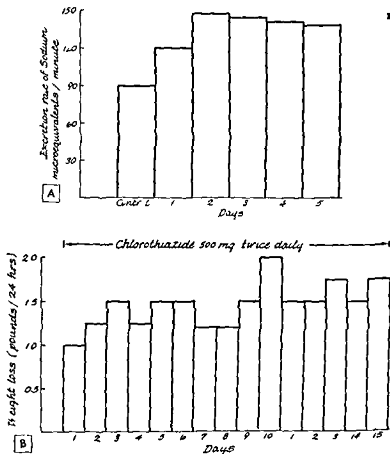


Fig 6 A When chlorothiazide is administered daily in a single 2000 mg oral dose the maximum rate of sodium excretion occurs on the second day and this high rate is maintained until body stores of sodium become depleted Observations made on a non cardiac patient maintained on a diet containing 150 mEq of sodium

B Weight loss in edematous patients parallels the increase in sodium excretion following the administration of chlorothiazide The diuretic response is maintained as long as the drug is given

inhibitors There is an increasing rate of bicarbonate and potassium excretion as the dose is increased

Since therapeutic doses of chlorothiazide do not appreciably increase bicarbonate excretion acidosis and resistance to the diuretic action do not develop on continued administration In a patient who received 2 gm of chlorothiazide orally at 6 A M for five consecutive days the maximal increase in the rate of sodium excretion occurred on the second day (Fig 6 A B)

CATIONS ANIONS

MICROEQUIVALENTS PER MINUTE

400
300
200
150
100
50
0

360 360

NH_3
K
Na

X
TITRATABLE ACIDITY
HCO_3
Cl

104 104

NH_3
K
Na

X
TITRATABLE ACIDITY
HCO_3
Cl

CONTROL DRUG CONTROL DRUG

X ANIONS WHICH WERE NOT ANALYZED

Fig 7 Average rate of excretion of various ions per minute after 2000 mg of chlorothiazide in a cardiac patient (based on a 24 hour urine collection)

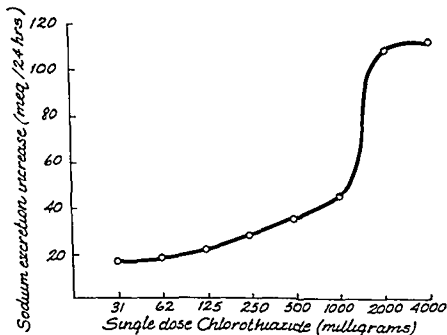


Fig 8 Dose-response curve from orally administered chlorothiazide in a patient with congestive heart failure

However there was a declining excretion of sodium on the fourth and fifth days as the body stores of this electrolyte were depleted This excretion rate of sodium gradually declined until it approximated the sodium intake and remained there as the patient approached dry weight

During the onset of diuresis from chlorothiazide there is no significant change in glomerular filtration rate or renal plasma flow Diuresis must therefore be attributed to an inhibitory effect on the mechanisms for absorption of water and electrolytes With large doses carbonic anhydrase inhibition undoubtedly is partly responsible for diuresis This mechanism probably has a minimal effect at the lower effective dosage levels

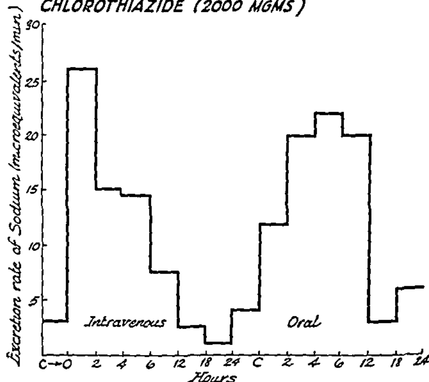


Fig 9 The onset of action is slower but more prolonged following the oral administration of chlorothiazide in comparison with an intravenous dose

Absorption The onset of action of chlorothiazide is prompt indicating rapid absorption from the gastrointestinal tract There is an increased diuretic and natriuretic response from this agent in patients as the oral dose is raised to approximately 4000 mg (Fig 8) Increasing the amount administered above this amount produces little additional effect The action persists for about 12 hours after oral administration

In a patient who received the drug at a dose of 1000 mg twice within a 24 hour period the increase in the excretion rate of sodium was repeated after the second dose in a fashion similar to that following the first dose but at a higher level and the total increase in sodium excretion per 24 hours was greater than after a single dose of 2000 mg It appears that when given every 12 hours the first two or three doses are cumulative but after that

continued administration of the drug does not produce a greater diuresis

In patients who received 2000 mg intravenously over a 60 minute period the pattern of sodium excretion was similar to that following the oral dose but was earlier in onset shorter in duration and hence less potent (Fig 9) In the absence of gastrointestinal disease the oral route of administration is to be preferred an attribute of note with any therapy requiring continuous drug administration

It is also noteworthy that the effect of chlorothiazide on sodium and potassium excretion is less from a single dose than from the same amount given in divided doses

Fate and Excretion Chlorothiazide disappears slowly from the plasma in nephrectomized dogs indicating that the compound may be partially transformed metabolically It has been isolated from the urine and feces so that degradation is not complete The rate of clearance by the kidney is greater than the glomerular filtration rate which indicates tubular secretion of the compound

Toxic Reactions Chlorothiazide is usually well tolerated Moderate muscular weakness and fatigue may appear initially, but these symptoms usually disappear with continued treatment Uncommon side reactions include muscle cramps giddiness and paresthesias

THE HYPOTENSIVE EFFECT OF DIURETICS

Recent interest in the hypotensive action of diuretics has developed because of the observation that chlorothiazide potentiates the action of ganglionic blocking drugs and indeed may lower blood pressure when given alone to hypertensive patients This effect of chlorothiazide has been ascribed to an action that may not be related to the diuresis evoked[1] Other oral diuretics have been reported to have no hypotensive action[1] Further investigation of this problem has demonstrated that oral mercurial diuretic therapy with chlormerodrin (Neohydrin) also potentiates the hypotensive action of ganglionic blocking agents[13] and it now is apparent that the hypotensive effect of mercurials is proportional to their natriuretic action[14] The hypotensive action of chlorothiazide may be reversed by an excess of salt in the diet The drug does not lower the blood pressure of normotensive patients[1]

The observation that dietary salt restriction enhances the hypotensive action of diuretics is additional evidence that this effect is due to increased sodium loss[16] Presumably sodium loss results in a reduction in interstitial fluid and plasma volume[15]

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A Review of Thiazide Derivatives

MORTON FUCHS TIBOR BODI AND SANFORD MALLIN

Hahnemann Medical College and Hospital

INTRODUCTION

The introduction of chlorothiazide as a potent oral diuretic agent has stimulated an intensive investigation of other thiazide derivatives for their diuretic activity

Ford *et al*[1] and other investigators have described the pharmacodynamics of chlorothiazide in detail Chlorothiazide has been shown to be an effective diuretic agent with its predominant action on sodium and chloride excretion and lesser effects on the potassium and bicarbonate ions The oral administration of chlorothiazide results in diuretic activity within two hours enduring for 6 to 12 hours and this agent appears to remain effective on continuous daily administration Oral doses are more effective for total 24 hour natriuresis than the rapidly excreted intravenous doses An oral dose of slightly more than 1000 mg is equivalent to 1 cc of merallunde (Mercuhydrin) administered intramuscularly

Clinical experience indicates that a 500 mg dose of chlorothiazide administered twice a day appears to be therapeutically adequate for controlling most cases of heart failure Natriuretic response increases progressively up to a dose of 2000 mg which appears to be the maximum effective dose doses in excess of 2000 mg do not demonstrate increased activity Toxicity with chlorothiazide has been manifested by minor gastrointestinal symptoms

such as anorexia nausea frequently in older age groups and an occasional rash However toxicity with this agent has been relatively unimportant up to the present time Occasional cases of thrombocytopenia have been seen Electrolyte imbalance with this agent as with any other potent diuretic may occur particularly deficiencies of sodium and potassium Again these deficiencies do not appear to have produced a major clinical contraindication to the use of chlorothiazide if adequate patient observation is maintained

The tremendous gain in diuretic therapy with chlorothiazide has prompted the evaluation of other benzothiadiazine derivatives in an attempt to improve the potency and decrease the incidence of side effects The following is a review of our experiences with trifluoromethylthiazide and hydrochlorothiazide

TRIFLUOROMETHYLTHIAZIDE (FLUMETHAZIDE [ADEMOL])

Trifluoromethylthiazide differs from chlorothiazide by replacing the chloride atom on the benzene ring by a trifluorinated methyl group This

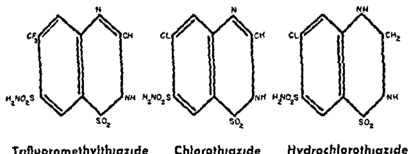


Fig 1 Structural formulas of three benzothiadiazine derivatives

drug can be administered orally and intravenously with minimal side effects as with chlorothiazide

Acute Response Study An evaluation of the effects of trifluoromethyl thiazide administered orally reveals similar responses in renal hemodynamics as with chlorothiazide Eight hundred mg of this agent was administered to eight patients These patients had normal renal function as evidenced by normal urinalysis and blood urea nitrogen levels Before administration of the drug control hourly urines were collected for sodium and potassium excretion and glomerular filtration rate was determined by inulin clearance and renal plasma flow established by para aminohippurate clearance techniques [2]

Following the administration of the drug the blood pressure was checked every few minutes for any immediate changes in blood pressure and then every 30 minutes for six hours There was no change in the mean blood pressure in any of the patients throughout the study (Fig 2)

The excretion of sodium is shown in Figure 3 The onset of natriuretic activity occurs between the first and second hours after administration of the drug and reaches its maximum effect by the end of the second hour The duration of activity appeared to persist past the sixth hour of the study

* Supplied through courtesy of E R Squibb & Sons

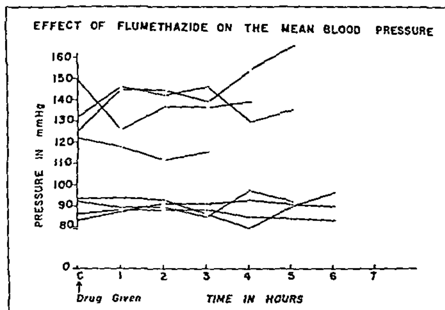


Fig 2 The mean blood pressure in eight patients after an oral dose of 800 mg of trifluoromethylthiazide There is no significant effect on the mean blood pressure in this group of patients (From Bodi *et al* To be published)

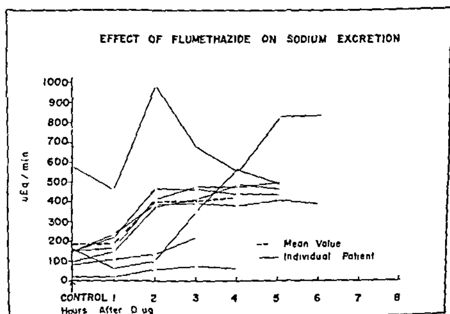


Fig 3 The mean value of sodium excretion after an oral do e of 800 mg of trifluoromethylthiazide The onset of increased sodium excretion occurred between the first and second hour after administration of the drug (From Bodi *et al* To be published)

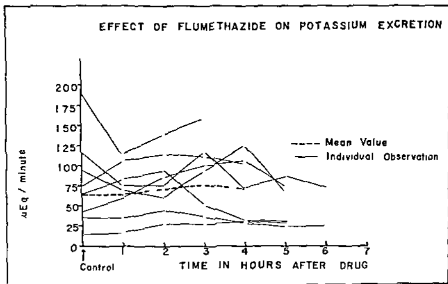


Fig 4 The mean value of potassium excretion after an oral dose of 800 mg of trifluoromethylthiazide There is no significant effect on potassium excretion (From Bodi *et al* To be published)

The excretion of potassium is shown in Figure 4 The mean value for the eight patients studied shows very little rise over the control values This study implies a difference in the kaluretic activity of chlorothiazide and trifluoromethylthiazide since chlorothiazide appears to have a more potent kaluretic effect which is a little less than one half its natriuretic effect

In six of the patients studied there was no significant change in either

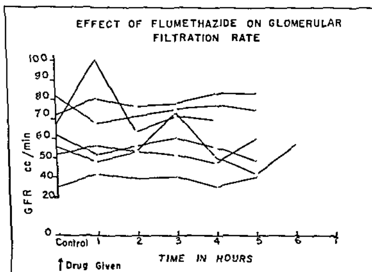


Fig 5 Glomerular filtration after oral trifluoromethylthiazide No significant effect is noted (From Bodi *et al* To be published.)

direction in the glomerular filtration rate over the period of study in this experiment (Fig 5) The seventh patient showed a temporary increase which may have been technical

In Figure 6 the renal plasma flow during the period of study in six patients is demonstrated There was no significant change in the renal plasma flow after the oral dose of 800 mg of trifluoromethylthiazide

Out Patient Study A dose response curve was determined in the out patient clinic by determining the acute weight response in 48 hours in a group of cardiac patients to increasing doses of the drug[3] The patients were free of diuretic therapy between doses of the drug for at least five days and were on maintenance digitalis therapy The dose response curve is presented

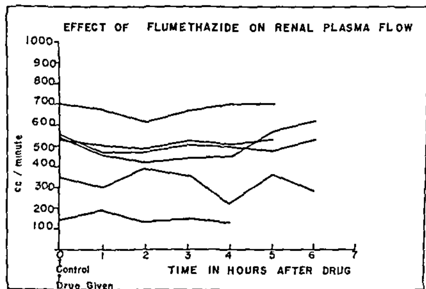


Fig 6 Renal plasma flow after 800 mg of trifluoromethylthiazide administered orally No apparent effect is noted in six hours of observation (From Bodi *et al* To be published)

in Figure 7 A dose of 800 mg twice a day had the same effect on weight response in this group of patients as did a dose of 500 mg of chlorothiazide twice a day in the same group of patients When 1000 mg is administered twice daily the effect is the same as that of 1000 mg of chlorothiazide twice daily Therefore the maximum effective dose of both drugs is the same Increasing doses above 1000 mg twice a day has no further increase in effectiveness as occurs with the chlorothiazide There is no explanation of the variance in dose response between the trifluorinated and chlorinated derivatives at the lower dose levels at this time

HYDROCHLOROTHIAZIDE

Hydrochlorothiazide differs from chlorothiazide by the addition of two hydrogen atoms to the one unsaturated bond in the heterocyclic ring

Excretion Studies The excretion rate of hydrochlorothiazide was determined in five normal subjects[4] as shown in Figure 8 Hydrochlorothiazide

[4] Supplied through courtesy of Merck Sharp & Dohme

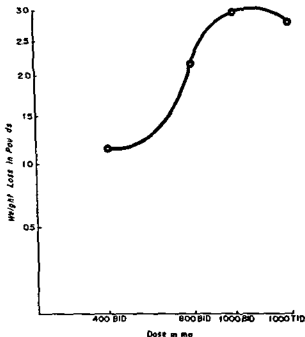


Fig 7 Dose response curve as determined by weight loss in 48 hours in a group of cardiac patients given increasing doses of trifluoromethylthiazide The maximum effective dose is 2000 mg Doses above this have no increased effectiveness (From Fuchs *et al* Am J Cardiol Submitted for publication)

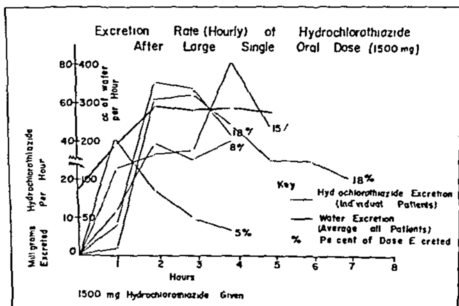


Fig 8 The excretion rate of hydrochlorothiazide in five normal subjects after oral administration of 1500 mg of hydrochlorothiazide At the end of six hours approximately 20 per cent of the drug was excreted in the urine The diuretic effect of the drug paralleled the excreting of the compound in the urine (From Moyer *et al* Am J Cardiol Jan 1959)

appeared in the urine within one hour after oral administration At the end of six hours approximately 20 per cent of the total administered dose of 1500 mg was excreted in the urine The disposition of the remaining drug was not determined Maximum excretion was reached within three hours after administration and the plasma level reached maximum concentration within the first two hours and rarely exceeded 6 mcg per ml of plasma This con

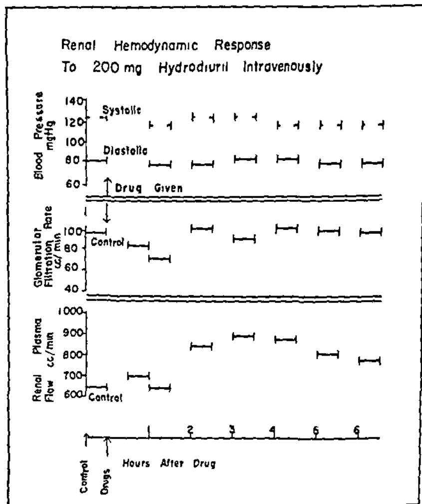


Fig 9 Renal hemodynamics following an intravenous dose of 200 mg of hydrochlorothiazide There was no effect on blood pressure but an initial fall in glomerular filtration rate was noted followed by a return to normal levels within one hour (From Moyer *et al* Am J Cardiol Jan 1959)

centration of the drug persisted throughout the period of observation suggesting continued absorption The diuretic effect of the drug paralleled the excretion of this compound in the urine

Studies after Intravenous Administration Hydrochlorothiazide was administered intravenously in a dose of 200 mg Observations were made on glomerular filtration rate by inulin clearance techniques and renal plasma flow was determined by para aminohippurate After three successive control

periods were obtained the drug was administered and successive 30 minute collection periods were made for five hours The results of the renal hemo dynamic studies are shown in Figure 9 Immediately following administra tion of the drug intravenously there was a temporary reduction in glomerular filtration rate This returned to control values within one hour Despite the temporary decrease in glomerular filtration rate there was an increase in salt and water excretion Para aminohippurate excretion (renal plasma flow) increased slightly It can be concluded from these observations that the diuretic and natriuretic effect of the drug is a tubular response and is not due to an increase in glomerular filtration rate A measurement of the hourly urine response following the administration of a large oral dose of the

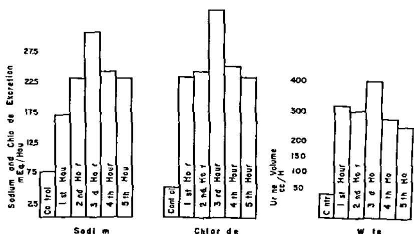


Fig 10 Measurement of hourly urine volume and sodium and chloride response following the oral administration of 1500 mg of hydrochlorothiazide A marked diuretic natriuretic and chloruretic response occurs in the first hour and persists throughout the observation period The maximum effect is noted in the third hour (From Moyer *et al* Am J Cardiol Jan 1959)

drug showed a diuretic response beginning in the first hour with the max imum response in the third hour and a diuretic effect throughout the observa tion period The same effect was demonstrated when the hourly increase in sodium and chloride excretion was compared with the control sodium and chloride excretion (*Fig 10*)

Electrolyte Response Curve In order to determine the degree of re sponse of electrolyte excretion to various doses of hydrochlorothiazide a group of 18 patients was used who had no cardiovascular or renal insuf ficiency These patients were then put on a 50 mEq sodium diet and control 24 hour urines were taken for several days until a fixed 24 hour sodium excretion (40 to 48 mEq) was obtained The patients were then given the drug for two days and 24 hour urines were collected for determination of increased sodium potassium and chloride excretion above control levels

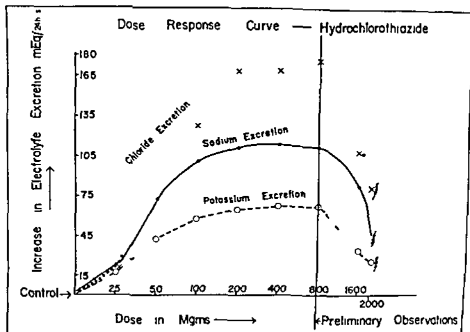


Fig 11 Dose response curve for sodium potassium and chloride after increasing doses of oral hydrochlorothiazide Activity occurs at 25 mg and increases to a maximum effective dose of 200 mg daily When doses above 800 mg are administered a blocking effect is noted (From Moyer *et al* Am J Cardiol Jan 1959)

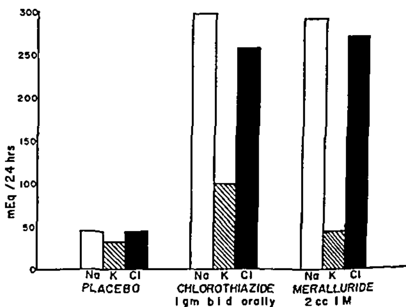


Fig 12 Electrolyte excretion response to chlorothiazide and a mercurial diuretic Sodium and chloride excretion are nearly similar

The average of the first 48 hours excretion was compared to the control The patients were then allowed to equilibrate and replenish the sodium stores again without the drug Increasing doses were administered after a period of equilibration was obtained for control sodium excretion The doses used were 25 mg 50 mg 100 mg 200 mg 400 mg 800 mg and 1600 mg per 24 hour period[5] The average excretion rate is graphed in Figure 11 It is noted that natriuretic activity occurs at the 25 mg level with a marked increase in electrolyte excretion up to 200 mg above which the increased response levels off At doses above 800 mg there appears to be a definite decrease in the excretion of sodium potassium and chloride demonstrating *a blocking effect and inhibition of electrolyte excretion In the*

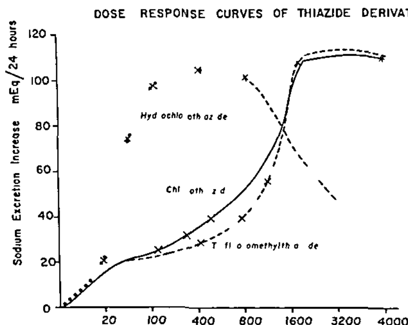


Fig 13 Dose response curve of the three benzothiadiazine derivatives The onset of natriuretic activity for hydrochlorothiazide is 25 mg and the maximum effective dose is ₋00 mg The onset of natriuretic activity of chlorothiazide and trifluoromethylthiazide is 250 mg and the maximum effective dose is 2000 mg For the effective dose range the dose of hydrochlorothiazide is approximately one-tenth that of the other two derivatives

effective dose range potassium loss is approximately one half that of sodium the most marked effect is on chloruresis which is greater than the natriuretic effect of hydrochlorothiazide This response is different from the response seen to chlorothiazide and a mercurial diuretic in which the sodium and chloride excretions are more nearly equal or the chloride excretion is less than sodium (Fig 12)

DISCUSSION

From the data presented above it appears that all three agents are efficient diuretic drugs A study of the dose response curves in Figure 13 reveals that the onset of activity of chlorothiazide and trifluoromethylthiazide starts

above the 250 mg dose level and increases to the maximum effective dose of 2000 mg The onset for hydrochlorothiazide starts at 25 mg and increases to a maximum effective dose of 200 mg Therefore in the effective dose range of these drugs a dose of hydrochlorothiazide is one tenth that of chlorothiazide or trifluoromethylthiazide However at the maximum effective dose levels the natriuretic effect is the same for all three drugs

Hydrochlorothiazide also differs from the other two derivatives in that there is a greater chloruretic than natriuretic effect and potassium excretion is active This could possibly lead to a hypochloremic hypopotassemic alkalosis Therefore close observation for electrolyte imbalance must be maintained with the use of this agent as with the use of any other potent drug The blocking effect of hydrochlorothiazide demonstrated at high dose

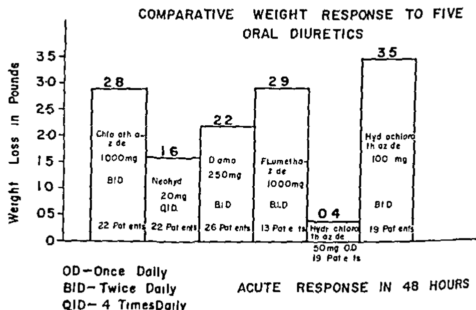


Fig 14 Comparative weight response to five oral diuretic agents The maximum effective doses of chlorothiazide and trifluoromethylthiazide are the same but less than that of hydrochlorothiazide

levels (above 800 mg) would imply a toxicity state probably at the renal tubular level and therefore doses greater than 200 mg a day should not be administered

A review of the clinical response to these agents demonstrates the acute 48 hour weight loss experienced in a group of congestive heart failure patients in our diuretic clinic (Fig 14) These patients were on maintenance digitalis therapy and were free of diuretic therapy for at least five days It is shown that the weight loss experienced by these patients is the same when the maximum effective dose of chlorothiazide and trifluoromethylthiazide is given This is greater than the response seen after the effective dose of chlormerodrin (Neohydrin) and acetazolamide (Diamox) is administered When the maximum effective dose of hydrochlorothiazide is given the weight response is greater than that with the other two thiazide derivatives, which could imply a greater clinical effectiveness

We have also seen rather efficient diuresis with hydrochlorothiazide in patients who have appeared refractory to chlorothiazide This may not necessarily imply a greater diuretic activity for hydrochlorothiazide but it may be a result of tolerance in those particular patients to chlorothiazide who are still responsive to hydrochlorothiazide If so then the factor of tolerance to one agent and not to the other may allow for more prolonged constant diuretic therapy by alternating the use of these agents before or after tolerance starts to manifest itself

Advancement in the diuretic field has been dramatic with the discovery of these agents and future increased benefits will be anticipated with the investigation of other derivatives of the benzothiadiazide structure

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Clinical Pharmacology and Use of Chlorothiazide in the Treatment of Hypertension

EDWARD D FREIS

Georgetown University School of Medicine

When chlorothiazide is administered to a nonedematous hypertensive or normotensive individual there is within the first 48 to 72 hours of treatment a diuresis of sodium and chloride with a loss of approximately 250 to 300 mEq of these ions over and above the level of intake The serum concentrations of sodium and chloride do not change significantly Accompanying the saluresis there is a loss of 1 5 to 2 5 kg of body weight and a reduction of extracellular fluid space of approximately 1 to 2 liters Thus the salt and body weight losses can be accounted for almost entirely by the reduction in extracellular fluid space [1]

Accompanying the loss of extracellular fluid space there is of course a reduction in plasma volume since these two spaces are in equilibrium The reduction in plasma volume averages about 400 *ml* a *15 to 20 per cent* reduction as has been shown by Dr Dustan s group at the Cleveland Clinic

and by ourselves All of these changes are well developed at the end of 48 hours of therapy It is during this period also that the blood pressure falls in hypertensive patients The extent of the hypotension is not great averaging 15 per cent of mean blood pressure In normotensive individuals despite similar fluid compartment changes there is no reduction of basal blood pressure although there is an alteration in vascular reactivity which will be described later

Crosley and his associates have shown and we have confirmed that the hypotensive response to chlorothiazide is associated with a decrease in right heart pressures and cardiac output Using the Hamilton method Dustan also has found a reduction in cardiac output It seems probable that the depletion of plasma volume and reduction of tissue pressure secondary to the interstitial fluid loss result in a fall of right heart filling pressures It is not easy to explain why these factors do not call forth compensatory reflex vasoconstriction Perhaps this failure is due to several factors The reduction in total blood volume is neither very great nor very rapid there is no loss of red cells and hemodilution cannot take place because of the concomitant depletion of the interstitial fluid space

If it is true that the reduction of arterial pressure is associated with a decline of cardiac output which in turn is dependent on the reduction of plasma volume then restoration of plasma volume should restore the arterial pressure When hypertensive patients are infused with 500 ml of 6 per cent dextran over a 15 minute period the blood pressure rises to or very close to the pre chlorothiazide level [3] The results are the same whether the dextran is dissolved in isotonic saline or in 5 per cent glucose in water Thus restoration of plasma volume rather than salt is essential for restoration of blood pressure

Addition of salt is effective in restoring the blood pressure only if enough is given to elevate the plasma and extracellular fluid volumes Since chlorothiazide is a highly potent saluretic agent about 25 gm of salt per day usually must be administered to produce the blood pressure reversal Only when the amount of salt is elevated to a point sufficient to produce a gain in body weight will the blood pressure rise also

These effects on plasma and extracellular fluid volumes are not temporary but continue as long as the drug is administered Measurements taken at 8 to 12 months following initiation of treatment show maintenance of some reduction in these extracellular spaces Discontinuation of chlorothiazide after these long periods of therapy results in a prompt restoration of extracellular volumes and of the blood pressure within 48 to 72 hours after the drug has been discontinued provided that adequate amounts of salt are permitted in the diet

The changes described are not unique for chlorothiazide Similar effects on blood pressure cardiac output and fluid volume compartments have been observed following parenteral mercurials In patients taking the rice diet for several weeks plasma volume depletion occurs and blood pressure can be restored either by supplying salt in the diet or by replenishing the plasma volume with salt free dextran [4] These various observations supply a unified coherent and rational paradigm in a formerly confused field The reason for the confusion in the literature [6] probably lies in the difficulties attendant on obtaining accurate volume space measurements Meticulous technique is required and even then frequent rechecks are essential in order to detect discrepancies For example we used two different indicators SCN and

radiosulfate or radiosodium together in tracing the extracellular volume changes and repeated the determinations when these were discrepant In regard to plasma volume the hematocrit change served as an additional check on the method

Although normotensive subjects respond to chlorothiazide with a similar saluresis and reduction of extracellular fluid compartments they exhibit no change in basal blood pressure However as Merrill[7] and ourselves[8] have shown the hypertensive response to norepinephrine infusion usually is reduced Contrariwise we have demonstrated that the hypotensive response to a depressor agent such as trimethaphan (Arfonad) is increased [8] Therefore although basal pressure is unaffected in normotensive subjects chlorothiazide alters their vascular responsiveness Their blood pressures become less reactive to pressor stimuli and more responsive to depressor agents

The basal blood pressure of the hypertensive is affected by chlorothiazide probably because some abnormal pressure mechanism is operative in these patients Chlorothiazide simply reduces their vascular reactivity to this unknown pressor mechanism Blood pressure was affected even in the mildest forms of hypertension with basal diastolics of 90 mm Hg and above These results speak against Pickering s concept that moderate degrees of elevated blood pressure do not reflect an abnormal disease process but represent rather the individuals at the higher ranges of the distribution curve of normal blood pressures [9] Our results with chlorothiazide indicate that at about 90 mm Hg basal diastolic pressure a clear cut separation exists between normal individuals and hypertensive patients

If the normotensive chlorothiazide treated subject is given 500 ml of salt free dextran in order to replenish his plasma volume the basal blood pressure does not change but the vascular responsiveness to pressor and depressor agents reverts immediately to the pretreatment level Therefore vascular reactivity is dependent in large measure on plasma volume

In previous studies on norepinephrine and ganglion blocking drugs [10] we pointed out the intimate relationship between total blood volume and the capacity of the vascular tree In that connection we emphasized the importance of the sympathetic nervous system in altering postarteriolar as well as arteriolar tone Sympathetic stimulation decreases peripheral vascular capacity and since blood volume remains unchanged central venous and right heart pressures rise with a resulting increase in cardiac output Sympathetic inhibition produces exactly opposite results with an increase in vascular capacity (in relation to effective blood volume) and a reduction in cardiac output

It would appear that salt depletion also affects the relationship between blood volume and vascular capacity in this case however by reducing effective blood volume rather than by increasing vascular capacity The same reductions are produced nevertheless in central venous pressure and cardiac output This of course explains why the combination of cholorothiazide and ganglion blocking agents has such great hypotensive potency These considerations do not rule out the possibility that arteriolar reactivity is unaffected by the reduced plasma volume Smooth muscle exhibits greater contractibility when it is stretched than when it is relaxed.

These studies also de-emphasize the importance of salt as an etiologic factor in hypertension It is true that salt deprivation or salt depletion reduces the blood pressure of hypertensive patients However this seems to be due primarily to the resulting fall in plasma volume Thus the role of salt in

hypertension appears to be permissive rather than causative If salt is available a normal expansion of extracellular and plasma volume is permitted thus allowing the unknown pressor mechanism in hypertension to function effectively

Chlorothiazide has been remarkable for the lack of uncomfortable side reactions and apparent freedom from toxic effects The reduction in extracellular fluid volume is in some way controlled at the desired level and does not proceed to the point of severe dehydration Yet a note of caution must be sounded Depressions of serum potassium levels have been noted by all observers in patients treated for long periods of time

Dr Wilson in our laboratory has studied some of the patients who have been under chlorothiazide treatment for periods of 8 to 12 months without potassium supplements In those with serum potassium levels below 3 5 mEq she found also reductions in total exchangeable potassium and elevations of total exchangeable sodium The latter occurred even though the extracellular fluid space remained reduced while the serum sodium concentration was essentially unchanged Therefore the excess exchangeable sodium must have been in the cells where it was replacing the cellular depletion of potassium This pattern is similar to that seen in chronic diarrheal states and may be a reflection of secondary aldosteronism stimulated by the reduction in cardiac output

Regardless of cause the reduction of total exchangeable potassium might have serious consequences over a long period of time Potassium supplementation in an amount of 75 to 100 mEq per day seems indicated in all patients who exhibit an abnormally low level of serum potassium It is hoped that this will be sufficient to maintain the patient in reasonably normal electrolyte balance Perhaps in the future aldosterone antagonists will be developed which will combat the depletion of body potassium

One could surmise from the alteration in vascular reactivity produced by chlorothiazide that the drug would be most effective in enhancing the antihypertensive action of other blood pressure reducing drugs Indeed this was the first observation made with this agent in hypertensive patients[11] Of the various antihypertensive compounds that can be used with chlorothiazide our experience indicates that hydralazine in doses not exceeding 150 mg per day is in general the most effective and best tolerated regimen for moderate hypertension In severe cases ganglion blocking agents with reserpine and chlorothiazide provide a potent and reasonably well tolerated combination Allowance however always must be made for problems posed by individual cases and the above regimens are suggested only as useful starting points in the therapeutic experiment posed by each patient

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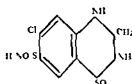
Hydrochlorothiazide in Hypertension

NEMAT O BORHANI
Johns Hopkins Hospital

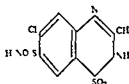
This is a preliminary report on the clinical trial of hydrochlorothiazide in a selected group of hypertensive patients in our Hypertension Clinic

Hydrochlorothiazide is a potent saluretic agent that resembles chlorothiazide qualitatively but is several times more active It can be used in several conditions in which chlorothiazide is successfully employed such as congestive failure edema and toxemia of pregnancy premenstrual tension cirrhosis and hypertension

Chemically hydrochlorothiazide differs from chlorothiazide in having no double bond in the heterocyclic ring Hydrochlorothiazide is the 3 4 dihydro derivative of chlorothiazide wherein the 3 4 double bond is saturated by two hydrogen atoms Its structure is represented as follows



Whereas the structure of chlorothiazide is as follows



Manufactured by Merck Sharp & Dohme as Hydrodiuril and by Ciba as Esidrex.

The synthesis of chlorothiazide in the Merck Sharp & Dohme laboratories by Novello and Sprague[1] and the discovery of its favorable saluretic action introduced a unique category of "benzothiadiazines to the management of cardiovascular renal disease In their extensive exploration of the benzothiadiazine chemistry Novello *et al* synthesized the dihydro derivative of chlorothiazide to which the name hydrochlorothiazide has been given On the basis of laboratory data hydrochlorothiazide is anticipated to be safe for clinical trial

METHODS

Thirty hypertensive patients with a history of congestive failure were selected from the general population of our Hypertension Clinic to determine the effect of daily administration of hydrochlorothiazide on blood pressure weight edema serum electrolyte changes and other clinical manifestations These patients were all taking one of the digitalis preparations daily and received no other medications (antihypertensive or otherwise) except hydrochlorothiazide The previous antihypertensive therapy on these patients included hydralazine ganglionic blocking agents chlorisondamine (Ecolid) mecamylamine (Inversine) and chlorothiazide (Diuril) Efforts were made to exclude the patients on whom any one of the Rauwolfia preparations was used prior to the beginning of this study One such case was found during the study and therefore was excluded The study was not set on "double blind" fashion in other words the patients were told of the nature of the new drug and the doctors were aware of the type of drug which was administered

The daily dose of the drug was 50 mg twice a day and it was uniformly so during the course of the study The serum electrolytes Na K Cl CO and BUN were measured at the beginning of the study and every four days thereafter The patients were allowed a liberal salt diet and no additional potassium preparations (including orange juice) were added to the diet

This study was carried out in the Hypertension Clinic exclusively The patients visited the clinic once a week during the period of the investigation On each visit to the clinic a complete physical examination was performed and the blood pressure was recorded on four different occasions with five minute intervals The mean systolic and the mean diastolic pressures before and after the study were compared

RESULTS

Table 1 shows a summary of the effect of the drug on the blood pressure of all these patients Mean systolic and mean diastolic blood pressures are compared before and after therapy with the difference on each occasion listed in the table Table 2 shows the results of the statistical analysis on these changes As is indicated in Table 2 these changes were statistically significant with a probability less than 0 01

Clinically all the patients showed some improvement Twenty three out of 29 patients improved considerably on this regimen

In the majority of these 23 patients the fall of blood pressure was accompanied by significant weight loss and saluresis The degree of weight loss was different in each patient It ranged between two pounds and 42 pounds

TABLE 1 EFFECT OF HYDROCHLOROTHIAZIDE ALONE ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE OF 29 AMBULATORY PATIENTS

NO	PATIENTS	MEAN SYSTOLIC B P BEFORE THERAPY	MEAN SYSTOLIC B P AFTER THERAPY	DIFFERENCE	MEAN DIASTOLIC B P BEFORE THERAPY	MEAN DIASTOLIC B P AFTER THERAPY	DIFFERENCE
1	B M	248.5	213	35.5	145	130	15
2	B D	239.5	209	30.5	147.5	113.5	34
3	B D	242	186.5	55.5	121	108	13
4	B J	195	151.5	43.5	131.5	116	15.5
5	C B	198.75	212.5	−13.75	121.25	122.5	− 1.25
6	E C	196	170	26	126.25	102.5	23.75
7	F H	187	154	33	127	117	10
8	G E	257.5	187.5	70	176	143.5	32.5
9	H R	183	157	26	151.25	145	6.25
10	K M	180	179	1	130	117	13
11	M C	165	170.5	− 5.5	107.5	110	− 2.5
12	M L	246.7	250	− 3.3	170	140	30
13	M T	242.5	205	37.5	102.5	106.5	− 4
14	M B	183.5	168	15.5	112.5	109	3.5
15	O H	163.75	134	29.75	113.75	112.75	1
16	P H	168.75	195	−26.25	110	122.50	−12.50
17	R J	196.25	187.50	8.75	125	117.50	7.50
18	S C	221	200	21	147.5	120	27.50
19	S J	229	184.50	44.50	144	120	24
20	S S	252.50	205	47.50	145	125	20
21	S L	172.50	157	15.50	104	91	13
22	S S	207.50	182.50	25	112.50	111	1.5
23	T P	249	252.50	− 3.50	151.75	150.50	1.25
24	W J	201	199	2	135	130.50	4.5
25	W C	245	22[illegible].50	22.50	157.50	167.50	−10
26	W L	237	255.50	−18.50	126	136.75	−10.75
27	W H	187.50	176	11.50	117	112.50	4.50
28	B G	186.50	133.50	53	121	108	13
29	H C	263.75	255	8.75	151.25	145	6.25

Rise in pressure (systolic or diastolic)

in five weeks The loss of weight was accompanied by no clinical ill effects except in one patient who was complaining of generalized weakness and who had a serum potassium of 3.2 mEq /L The serum electrolyte showed some remarkable changes during this study which was mainly on the sodium ion The loss of sodium was usually accompanied by weight loss and a fall in the blood pressure This observation was not, however uniformly noticed throughout the study Some patients showed a fall in blood pressure with

TABLE 2 STATISTICAL ANALYSIS OF 29 AMBULATORY HYPERTENSIVE PATIENTS RECEIVING HYDROCHLOROTHIAZIDE ALONE

	MEAN SYST B P	MEAN DIAST B P
Before therapy	211.92	130.2[illegible]
After therapy	191.48	120.27
Mean of difference	20.4	9.65
Standard error of the mean	4.3	2.4
t	4.7	4.0[illegible]
P	<0.01	<0.01

Statistically significant.

little or no change in weight and serum sodium content. There were no significant electrolyte disturbances in these patients. The serum potassium in most of the patients was either unaltered or dropped slightly. No patient at any time developed potassium depletion. The lowest serum potassium recorded was 3.2 mEq./L., which was corrected by the administration of two glasses of orange juice every day for one week.

SUMMARY AND CONCLUSION

Hydrochlorothiazide is a new oral diuretic similar to and more active than chlorothiazide. With a daily dose of 100 mg. per day we were able to obtain a good diuretic, saluretic and antihypertensive effect in 23 out of 29 hypertensive patients receiving this drug for a period of four months. This result was clinically and statistically significant ($p<0.01$).

The place of hydrochlorothiazide in the treatment of congestive failure and hypertension should certainly be investigated more thoroughly. A double blind comparison study to compare the effect of chlorothiazide and hydrochlorothiazide on a group of hypertensive patients is at the present time underway in our clinic; until such a study is completed and the results evaluated, we do not feel justified in advocating the use of hydrochlorothiazide in the treatment of hypertension.

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Observations on the Role of Chlorothiazide as Related to the Treatment of Hypertension—Observations on the Mechanism of Action

ARTHUR GROLLMAN

University of Texas, Southwestern Medical School

The demonstration of the potent natriuretic action of chlorothiazide (Diuril)[1] and the established hypotensive action of sodium restriction suggested early the use of this drug in the treatment of hypertension as a substitute for or in conjunction with sodium restriction. The relative lack of toxicity of this compound when used in moderate doses and its demonstrated

effectiveness as a hypotensive agent soon led to its widespread use either alone or in combination with other available hypotensive agents [3] Other diuretics such as ammonium chloride and the mercurial diuretics had been advocated in the treatment of hypertension but received little application because of the undesirable side effects of the former and the potential toxic effects of the latter when used in adequate doses for prolonged periods

The diuretic action of chlorothiazide and its potent saluretic activity as well as its activity as an inhibitor of carbonic anhydrase are well established [4] It induces chloruresis in a manner analogous to that of the mercurial diuretics Since it is a potent inhibitor of the renal tubular reabsorption of sodium and causes a considerable increase in the excretion of chloride with minimal increases in the excretion of bicarbonate and potassium it acts essentially in a manner similar to that of drastic sodium restriction It has been claimed by some that chlorothiazide given alone reduces the blood pressure appreciably in hypertensive patients but this has been denied by others It is generally accepted however that when used in combination with other forms of antihypertensive therapy there is an augmentation of the blood pressure response to other hypotensive drugs including the ganglionic blocking agents Rauwolfia derivatives Veratrum alkaloids and hydralazine This activity is observed regardless of whether or not congestive heart failure is present

In order to determine the mechanism of action of chlorothiazide in lowering the blood pressure its effects on electrolyte excretion have been correlated with its hypotensive action in experimentally induced hypertension in rats and in patients with essential hypertension who had been followed for a number of years on sodium restriction By altering the electrolyte intake it was possible to compare the hypotensive effects of chlorothiazide (and some of its more recently introduced congeners) with that induced by comparable losses of sodium induced by dietary restriction alone

Chlorothiazide when administered in relatively large doses (0 5 gm) to hypertensive rats on their normal diet is capable of reducing the blood pressure to a degree comparable to that attained by drastic sodium restriction The two procedures are synergistic and the hypotensive action and its degree are accelerated and intensified when both are utilized together Conversely the addition of sodium chloride to the diet in an amount equivalent to that excreted under the influence of the drug prevents the observed decline in blood pressure

Likewise in human patients whose blood pressure had been reduced by a drastically restricted sodium intake it was possible to increase the dietary sodium intake without increasing the blood pressure if chlorothiazide was administered in doses sufficient to cause the loss of the sodium added to the diet

Arguments have been advanced to indicate that chlorothiazide has a unique antihypertensive action which is not dependent at least entirely on its diuretic effects These arguments are that (1) chlorothiazide is not hypotensive in normal subjects regardless of whether they are in congestive heart failure or not and whether or not diuresis is induced (2) the drug induces a greater and more rapid antihypertensive effect than salt restriction and (3) other potent diuretic agents have only a mildly antihypertensive effect However none of these arguments are cogent Sodium restriction like chlorothiazide does not reduce the blood pressure of normotensive individuals

Hollander and his associates have demonstrated that both chlorothiazide and meralluride when injected intravenously are ineffective in lowering the blood pressure of normal subjects and induce an equal effect in hypertensive subjects However since the action of chlorothiazide includes an increased loss of potassium acute depletion of this ion may contribute to the observed decline in blood pressure[6] if not compensated for by an adequate potassium intake

The controversy as to whether or not chlorothiazide alone can exert any hypotensive activity must be answered in the affirmative However this requires excessively large doses of the drug unless the sodium intake is simultaneously reduced Hence the effectiveness of chlorothiazide depends upon the concomitant degree of salt restriction

It would appear from our experiments that chlorothiazide exerts its antihypertensive action primarily by its natriuretic action, although potassium depletion and other dislocations of acid base and electrolyte equilibrium which occur concomitantly may contribute to the observed action of the drug when used in large doses as compared with sodium restriction alone

As regards the mechanism of the antihypertensive effect of chlorothiazide or of sodium restriction this is apparently due to the decrease in plasma volume and extracellular fluid volume induced by these procedures The secondarily induced electrolyte disturbance in the tissues although slight may contribute to this action The fact that the addition of sodium chloride to the diet prevents the hypotensive action of chlorothiazide indicates the prepotent effects of sodium loss in eliciting this action Whether or not the drug alone will lower the blood pressure depends upon the dosage used and the sensitivity of the individual to the effects of sodium restriction which is known to be exceedingly variable in different patients

Although when given in a single dose chlorothiazide produces its diuretic effect within two hours its effect on the blood pressure is not noted for some days This speaks against the hypotensive action being due to a direct vascular effect but rather to its cumulative effect on electrolyte excretion Beavers and Blackmore[7] have demonstrated that the response to injections of norepinephrine epinephrine and isopropyl norepinephrine in the anesthetized dog are modified by the prior injection of chlorothiazide Such experiments however cannot be accepted as evidence for a direct vascular effect of the drug under clinical conditions

In view of the difference in the mechanism of action of chlorothiazide as compared to ganglionic blocking and other hypotensive drugs it is to be anticipated that when the latter are given in conjunction with chlorothiazide smaller and less frequent doses are needed Sodium restriction, likewise acts synergistically with hypotensive drugs or with sympathectomy to reduce the blood pressure in the hypertensive

The effectiveness of chlorothiazide in patients refractory to other forms of therapy is further evidence for the efficiency of salt restriction as a means of lowering the blood pressure The failure of many to obtain satisfactory results by dietary means alone and the unpopularity of the dietary management of hypertension reflect the practical difficulty of restricting the dietary sodium intake Since chlorothiazide or its congeners induce a decline in blood pressure with a less arduous dietary restriction of sodium these drugs afford a practical method for attaining the hypotensive action of drastic sodium restriction By partially restricting the sodium intake minimal

doses of the drugs can be used thereby avoiding the potential dangers inherent in their prolonged use in large amounts

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Discussion

Calvin Kay *Moderator*
John Beem
Karl Beyer
William Daeschner
Harriet Dustan
Ralph Ford
Edward Freis
Robert Gaunt
Ray Gifford
Arthur Grollman
Carroll Handley
William Hollander
Sibley Hoobler
George Meneely
Lewis Mills
Marvin Moser
William Paton
Bertram Winer

Dr Kay I am unable to detect among our panelists any major disagreement about the role of salt and diuretics in the therapy of hypertension The listener is forced to several conclusions by the evidence presented First sodium depletion by dietary restriction or by saluresis reduces the blood pressure in hypertensives—but little if at all in normotensives However both normotensives and hypertensives after salt depletion become less susceptible to pressor agents and more susceptible to depressor agents Second these effects may be negated with sodium repletion or the administration of dextran These observations and results of direct measurements of the plasma volume and the extracellular fluid lead to the conclusion that plasma volume reduction is the principal and perhaps the only mechanism by which sodium depletion works Third the hypotensive action of sympathetic blocking agents may be similar in mechanism by increasing the peripheral vascular capacity which in effect simulates a decrease in plasma volume Finally these effects mediated by a reduction of plasma volume are presumed to diminish vascular reactivity to an unknown pressor substance or substances and to provide the basis of salt depletion as an essential adjuvant to depressor drug therapy

Dr. Winer At present I do not believe the effect of chlorothiazide is solely a volume mechanism In my own study of chlorothiazide certain

patients had a marked fall in plasma volume and exchangeable sodium and no change in blood pressure Other patients had a blood pressure reduction without a diminution of plasma volume and exchangeable sodium The correlation coefficient was very low for change in exchangeable sodium with change in blood pressure It was also low for change in exchangeable potassium or change in plasma volume Inconsistencies in the available data make me hesitant to accept plasma volume as the sole mechanism

In certain patients responsive to chlorothiazide the administration of 8 to 12 gm of salt a day may increase the 24 hour urine sodium from 100 to 150 milliequivalents of sodium to 300 or 350 milliequivalents of sodium Nevertheless in ten such patients the blood pressure did not rise during the administration of salt These patients were receiving a gram and a half of chlorothiazide a day This is a substantial dose Perhaps this is the reason their blood pressure did not rise However, the evidence is not completely consistent with your summary

Dr Kay May I have someone convert the 8 to 12 gm of additional salt to milliequivalents for comparison with the urinary excretion of sodium referred to?

Dr Winer The additional sodium excreted was approximately equivalent to the added salt ingested

Dr Kay Someone in the audience has asked if chlorothiazide results in reduction of blood pressure in bilateral nephrectomized dogs and if so, how this is related to the sodium theory The study of blood pressure in a nephrectomized animal is very complex

Dr Dustan Some of Dr Winer s results are inconsistent All biologic observations are characterized by variability and research results are usually inconsistent in part especially in the human species in which rigidly controlled conditions are less feasible However as Dr Freis has pointed out the trends in such results may indicate the mechanism acting in most of the patients or the majority of the experimental animals Inconsistencies in results indicate avenues for further research However is it not exciting that utilizing chlorothiazide as a research tool the results now suggest that it is the volume which is important and not the sodium ion *per se*?

Dr Hollander In eight of the twelve subjects studied by Drs Wilson and Freis there occurred little or no change in plasma volume would that not suggest to you that some other factors are involved in the hypotensive action of chlorothiazide? I believe however that Dr Freis and I are now in almost complete agreement as to the mechanism of action of chlorothiazide We agree that a high salt intake does not block the antihypertensive action of chlorothiazide and that chlorothiazide is capable of reducing blood pressure in the presence of normal values for body sodium body potassium extracellular fluid volume and plasma volume These results suggest that other factors are operating in the antihypertensive action of chlorothiazide Chlorothiazide may act by shifting electrolytes and water in local tissues

Dr Kay Might this be a specific effect of chlorothiazide upon the tissues

or vessels concerned? I know you are referring to vessels when you say tissues

DR HOLLANDER I don t know We plan studies in the future to determine the answer

DR KAY Dr Freis do you agree with Dr Hollanders statements?

DR FREIS First let me answer Dr Winer It is true that some hypertensive patients do not have a reduction in blood pressure with chlorothiazide That probably means the mechanism of hypertension is different in some patients than it is in others However the majority of hypertensives show some reduction of blood pressure Unlike Dr Winer I have not seen the blood pressure fall in the absence of a change in plasma volume In addition there is a trap in equating total exchangeable sodium determinations with extracellular fluid volume After a patient has been treated for a long period of time sodium enters cells as they become potassium depleted Total exchangeable sodium determined one or two months after initiating therapy with chlorothiazide is apt to be normal or increased depending upon the depletion of potassium occurring during that period

Finally in regard to salt loading I do not think you gentlemen gave enough salt Chlorothiazide is a very efficient saluretic agent and we found except for our first patient who required only 11 gm that 25 gm or more of salt a day was necessary in an effort to reverse the antihypertensive effect of chlorothiazide Then when the patient gained weight showing that salt ingestion had begun to exceed the saluretic effect of the chlorothiazide the blood pressure rose Therefore Dr Hollander our results do not agree with your statements Also Dr Hollander there was some reduction of plasma volume in all except three of our patients It was not very great however the interpretation is difficult because after eight or twelve months of therapy you cannot be sure the blood pressure level recorded is still due to the drug that you gave I frequently have seen other agents for example ganglion blocking agents continued with a disappearance of the signs of ganglionic blockade after eight or twelve months and yet the blood pressure is still reduced I suspect that such a patient has become relatively tolerant to the ganglion blocking effects of the drug but that his blood pressure has been reset at a lower level Indeed upon withdrawal of the drug in some of those people the blood pressure will remain down Therefore it is inaccurate to attribute to a drug the reduction of blood pressure eight or twelve months after initiating a therapy

DR MENEELY None of the available methods for determining plasma volume or extracellular fluid are very reliable I wonder if a shift of sodium into or out of cells may not result in apparent changes in extracellular fluid

DR GIFFORD I have observed a group of 81 hypertensive patients to whom we have given chlorothiazide and, in general the weight reduction and the reduction of blood pressure were closely correlated both as to the time of onset and to the degree We have not found it necessary to restrict sodium to get this reduction in blood pressure We made no efforts to see how much sodium a patient can tolerate however After a patient has been on chlorothiazide for some time and the drug is then withdrawn the blood pressure

does rise for approximately two weeks at which time the weight also will rise a pound or two

DR FREIS That is what I was trying to bring out I think you modify the basal level of blood pressure with prolonged therapy

DR KAY Dr Freis if sodium is trapped within cells may the administration of potassium promptly exchange intracellular sodium and result in a saluresis and diuresis in such individuals?

DR FREIS We are studying this problem now and I don t know the answer yet

DR KAY Do other panelists agree that there probably is some intracellular sodium migration?

DR HOLLANDER Some of our patients had an increase in body sodium of about 125 to 150 milliequivalents and others had a reduction in body sodium Statistical analysis of the data revealed no significant change in body sodium I would like to know if Drs Dustan and Freis have found a reduction of body weight upon prolonged chlorothiazide treatment in combination with other drugs

DR DUSTAN These patients have an initial weight reduction thereafter on maintenance treatment it is rather hard for me to interpret subsequent weight changes because other variables such as dietary habits must be considered

DR FREIS Uniformly there is a weight reduction when therapy is commenced Some patients regain their weight and some do not Upon withdrawal of the drug and administration of salt they regain within 48 hours a few pounds approximately the same amount they lost initially This suggests a depletion somewhere Why these patients regain weight I dont know but I don t think it means that the drug was acting in one way to lower blood pressure the first week it was given and an entirely different way after three or four months of treatment

DR MENEELY In experimental hypertension produced in rats we have observed some rats ingest large quantities of salt and have marked hypertension and increased total exchangeable sodium whereas other rats eat moderately increased quantities of salt have moderate elevation of blood pressure and no increase in total exchangeable sodium Probably the human species has similar biologic variation There are many as yet inexplicable observations in this whole field that is rats fed a high sodium and low potassium diet have an increased rather than a diminished total exchangeable potassium

DR. HOOBLER Why Dr Freis do some patients lose weight and yet have no reduction of blood pressure? Similarly have you observed in some patients a reduction of plasma volume and a failure of blood pressure reduction? If so how do you explain this?

Dr Freis There are two groups of hypertensive patients one responsive by blood pressure reduction the other nonresponsive Failure of the moderator responses must be involved The normal individual upon diminution of plasma volume immediately has stimulation of his moderator responses whereby compensatory vasoconstriction and venoconstriction restore cardiac output and arterial pressure For some reason some hypertensive patients do not make that adaptation

Dr Kay Apparently the sodium depletion phenomenon is no correlative of "Peter and the Wolf wherein elevation of the wolf's feet off the ground was fine in every way yet anything short of that was worthless In other words this is a problem in that there are varying degrees of response in the same patient depending upon the extent of sodium depletion The blood pressure response may approximate a linear function perhaps related to plasma volume or perhaps to weight

Dr Gaunt Perhaps Dr Grollman can tell us if this generalization is true Initial potassium depletion reduces blood pressure whereas chronic potassium depletion tends to increase blood pressure as a result of associated renal damage If this is true how long does the depressor effect last? Is potassium depletion if and when it occurs during chlorothiazide administration a limiting factor in the antihypertensive effect of that drug?

Dr Grollman There is a paradoxical effect of potassium depletion but the time limits appear to be very indefinite Hypertensive animals have a blood pressure reduction when placed on a diet very deficient in potassium If this is done during early life in rats blood pressure remains normotensive at the time of weaning However kidney injury and subsequent hypertension develop I do not think as you insinuated that this potassium defect accounts for some of these discrepancies that we have been talking about

Dr Gifford Do you Dr Grollman believe sodium depletion to be one of the first therapies indicated in the treatment of hypertension and if so how much do you restrict sodium intake in patients receiving chlorothiazide and in patients not receiving chlorothiazide?

Dr Grollman Chlorothiazide makes it unnecessary to restrict salt intake markedly as was formerly necessary We now allow patients a 2 to 3 gm sodium diet which is quite acceptable to them Formerly before chlorothiazide became available we restricted salt to 0 5 to 1 0 gm or less depending upon the response which was greatly variable among patients and sometimes the response was unsatisfactory even with this restriction

Dr Gifford How much chlorothiazide do you use then?

Dr Grollman The amount required to give an optimal response is often between 0 5 gm and 1 gm daily rather than larger amounts sometimes necessary to control edematous states We have a large variable to consider in that patients may eat 5 to 30 gm of salt daily The average may be as much as 15 gm daily Therefore obviously the results of chlorothiazide may vary considerably in accord with the amount of salt ingested

DR HANDLEY What is Dr Freis explanation for a depressed response to the infusion of norepinephrine and an increased response to trimethaphan after chlorothiazide administration in normotensive individuals?

DR FREIS We think this is a result of plasma volume reduction because restoration of plasma volume reverses the response to control values Filling pressure of the right side of the heart and cardiac output are related to this probably

DR FORD Do we agree that the antihypertensive effect of chlorothiazide is shared with any chemotherapeutic agent with equivalent saluretic potency?

DR KAY A very good question

DR HOLLANDER Would you mention the compounds which you have in mind?

DR FORD Meralluride triazine diuretics hydrochlorothiazide

DR HOLLANDER These compounds have different diuretic potencies

DR FORD At equipotent natriuretic dosage of course

DR HOLLANDER Parenteral mercurial diuretics may reduce blood pressure but acetazolamide chlorazinil and aminophylline administered orally individually or in combination do not reduce blood pressure This does not answer your question however

DR FREIS If you do not obtain a very good saluretic effect reduction in blood pressure does not occur

DR HANDLEY The blood pressure reduction is proportional to the output of salt irrespective of what compound you use

Combined Drug Therapy of Hypertension Methodology of Treatment with Sympathetic Depressants and Diuretics

RAY W GIFFORD JR

*Mayo Clinic and Mayo Foundation**

Until recently effective drug therapy for hypertension depended entirely on agents which depress the sympathetic nervous system (Table 1) When used alone or in combination these drugs usually reduce blood pressure but they also produce side effects that are frequently unpleasant and sometimes serious

A welcome innovation to antihypertensive therapy has been the use of a potent oral diuretic chlorothiazide (Diuril)[1-3] This drug is not a sympathetic depressant yet it is mildly hypotensive in its own right and it definitely enhances the action of drugs that do inhibit the sympathetic nervous system The hypotensive properties of chlorothiazide are apparently due to the nonspecific effect of diuresis with consequent reduction of the volume of extracellular fluid and plasma[4] Other potent diuretics seem to be equally effective[5,6]

Since chlorothiazide rarely produces annoying side effects and since its use frequently permits reduction in doses of antihypertensive drugs that do combination therapy with this drug included often leads to better control of hypertension with less discomfort to the patient

CHLOROTHIAZIDE AS A HYPOTENSIVE AGENT

The results of treatment of 81 hypertensive patients at the Mayo Clinic with chlorothiazide alone or in combination with a sympathetic depressant agent are shown in Table 2 Data on these cases are to be published in greater detail elsewhere[7] but will be mentioned here

Chlorothiazide Alone When used alone in doses of 500 mg from one to three times daily chlorothiazide induced some reduction in blood pressure for most of the hypertensive patients in this series Chlorothiazide alone was sufficient treatment for about 30 per cent of the patients with mild hypertension The remainder required the addition of one or more sympathetic depressant drugs for adequate control of blood pressure

Chlorothiazide and Ganglion Blocking Drugs A combination of chlorothiazide and a ganglion blocking agent is the most potent antihypertensive weapon available at this time In fact it is so potent that the addition of chlorothiazide to the regimen of a patient already taking a ganglion block

* The Mayo Foundation Rochester Minnesota, is a part of the Graduate School of the University of Minnesota

TABLE 1 SITE OF ACTION AND SUGGESTED DOSES OF SYMPATHETIC DEPRESSANT DRUGS

Drugs: Nonproprietary name	Drugs: Trade name	Suggested daily dose, mg	Doses per day
Central acting drugs			
Rauwolfia			
Rescinnamine	Moderil	0.25–1.0	1–4
Reserpine	Serpasil, Reserpoid, Sandril, Serpiloid	0.1–0.5	
Deserpidine	Harmonyl	0.25–1.0	
Syrosingopine	Singoserp	0.5–2.0	
Alseroxylon fraction	Rauwiloid	2.0–8.0	
Whole root	Raudixin	100–500	
Veratrum			
Alkavervir	Veriloid	8–24	3 or 4 (p.c. and h.s.)
Cryptenamine tannate	Unitensen tannate	8–24	
Protoveratrines A and B	Provell, Veralba	0.8–3.0	
Hydralazine hydrochloride	Apresoline	40–300	2–4
Drugs acting on autonomic ganglia			
Ganglion blocking drugs			
Hexamethonium chloride	Hexameton or Methium	500–6000	2–4 (a.c. and h.s.)
Pentolinium tartrate	Ansolysen	80–2000	
Chlorisondamine chloride	Ecolid	40–800	
Mecamylamine hydrochloride	Inversine	5.0–120	
Trimethidinium methosulfate	Ostensin	40–400	

ing agent frequently will cause hypotension with orthostatic syncope within 24 to 96 hours unless the dose of the ganglion blocking drug is reduced before any chlorothiazide is given. After several experiences with orthostatic syncope my colleagues and I learned that the dose of ganglion blocking agent should be reduced routinely by approximately 50 per cent one or two days before treatment with chlorothiazide is started. For most patients this reduction or a larger one can be permanent because of the augmentation of ganglionic blockade by chlorothiazide. For 20 of the 24 patients in the

TABLE 2 RESULTS OF TREATMENT OF HYPERTENSION WITH CHLOROTHIAZIDE ALONE OR IN COMBINATION WITH SYMPATHETIC DEPRESSANT DRUGS IN 81 CASES

Sympathetic depressant drugs	Patients	Average blood pressure: Before chlorothiazide	Average blood pressure: With chlorothiazide	Per cent of patients responding with reduction of mean B.P. of: <10 per cent	10–20 per cent	>20 per cent
None	38	187/111	166/102	50	47	3
Ganglion blocking agent	24	184/112	155/99†	29	58	13
Hydralazine	9	179/97	151/85	22	56	22
Rauwolfia	10	185/105	162/97	50	40	10

$$\text{Mean blood pressure} = \frac{\text{Systolic} + \text{diastolic}}{2}$$

† Dose of ganglion blocking agent reduced in 20 of the 24 cases

series who received this drug it was possible to make a permanent reduction in the dose of ganglion blocking drugs when chlorothiazide was added to the regimens and at the same time further significant reductions in blood pressure were achieved for 70 per cent of these patients (Fig 1) Nearly half of the 24 patients were rendered normotensive by this combination while they were taking an average of only 50 per cent as much ganglion blocking agent as they took before chlorothiazide was added It takes little thought to deduce the relief from side effects which reductions in dose of this magnitude afford Grateful indeed is the patient whose unpleasant symptoms from treatment with drugs disappear while his hypertension improves yet chlorothiazide has wrought this miracle for many patients who previously have had to resort to large doses of ganglion blocking drugs for adequate control of hypertension

Chlorothiazide and Hydralazine Next in order of potency is the com

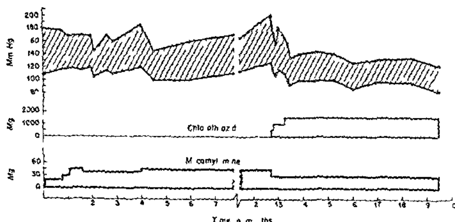


Fig 1 The addition of chlorothiazide to mecamylamine achieved normotensive levels of blood pressure for a 46 year-old woman with hypertension group II Decreasing the dose of mecamylamine at the time that administration of chlorothiazide was started in smaller than usual doses avoided orthostatic hypotension The 33 per cent reduction in dose of mecamylamine was permanent in this case

bination of chlorothiazide and hydralazine From the data presented in Table 2 the potency of this combination appears almost equal to that of chlorothiazide and a ganglion blocking drug However the patients who received hydralazine had less severe hypertension and the addition of chlorothiazide permitted reduction in the dose of hydralazine for only two of the nine patients Nevertheless I am confident that treatment with hydralazine and chlorothiazide has controlled the hypertension of many patients who would have required ganglion blocking drugs before the advent of chlorothiazide

Chlorothiazide and Rauwolfia Least potent, in my experience is the combination of chlorothiazide and Rauwolfia

Chlorothiazide and Veratrum. Reports of other investigators[1, 2] indicate that chlorothiazide also enhances the hypotensive effect of Veratrum My experience in using this combination has been too limited to warrant comment.

Side Effects of Chlorothiazide

Unlike other hypotensive agents chlorothiazide produces few unpleasant symptoms Occasionally patients complain of weakness fatigue and bad taste which cannot be related to hypotension or hypokalemia A few have experienced gastrointestinal irritation as manifested by nausea abdominal pain bloating or diarrhea but stopping treatment because of these side effects rarely has been necessary

Potentially more serious are the disturbances of blood electrolytes which have been observed at one time or another in about 50 per cent of the patients taking chlorothiazide

Abnormally high values for blood urea were observed at least once during treatment with chlorothiazide for 23 per cent of patients who had normal values before treatment was started[7] Only 4 per cent of hypertensive patients treated with sympathetic depressant drugs without chlorothiazide had elevated values for blood urea during the period of treatment

Values for blood urea increased significantly for half of the patients who had elevated values before treatment with chlorothiazide and for some of these the concentration of urea increased rather promptly to alarming levels For this reason chlorothiazide should be administered with extra caution if at all to patients with renal insufficiency and azotemia

Approximately 40 per cent of patients exhibited less than 3 5 mEq of potassium per liter of serum on one or more occasions during treatment with chlorothiazide For approximately 12 per cent the level of serum potassium decreased to less than 3 0 mEq per liter

For most patients the elevation of blood urea and the hypopotassemia caused no symptoms and they would have escaped detection except for the routine determinations of urea and potassium Since the abnormalities in urea and potassium usually appeared in the first two weeks of treatment it seems advisable to determine the urea and potassium at the end of two weeks and again at the end of the first month of treatment Determinations should be made as often thereafter as the previous values and the clinical course of the patient indicate

Frequently low values for serum potassium and elevated values for blood urea will spontaneously return to or toward normal in spite of continued administration of chlorothiazide Sometimes reduction in the dose of chlorothiazide will correct these abnormalities Some patients however who have been observed carefully at the Mayo Clinic consistently exhibited 50 to 70 mg of urea per 100 cc of blood (normal is 40 mg per 100 cc or less) or 3 0 to 3 5 mEq of potassium per liter of serum or both as long as chlorothiazide was being given These persistent abnormalities are a source of some concern relative to the possibility of renal damage produced by prolonged administration of chlorothiazide However so far as I can determine these mild deviations of blood urea and serum potassium from normal cause no symptoms and do not lead to irreversible damage to organ systems at least for periods up to 12 months

The indications for administering supplementary potassium to patients who are taking chlorothiazide are listed in Table 3 In spite of these rather numerous indications most patients taking chlorothiazide do not require supplementary potassium Nevertheless there is no objection to its routine use provided that the physician is not lulled into a false sense of security

for potassium chloride in doses of 1 gm three times daily or potassium triplex in doses of 4 cc three times daily failed to correct or prevent hypokalemia for nearly a third of patients[7] who were so treated in my series For this reason larger doses are recommended (Table 3) however symptomatic hypokalemia with serum levels of potassium of less than 3 0 mEq per liter developed in only one patient in my series a man with severe chronic renal insufficiency while he was taking supplementary potassium

The rapidity with which symptomatic hypokalemia developed in several patients who were receiving chlorothiazide when they became acutely ill or during a postoperative period leads me to speculate that total body stores of potassium may be depleted to a greater extent than the serum values would indicate

TABLE 3 INDICATIONS AND SUGGESTED DOSES FOR USE IN ADMINISTERING SUPPLEMENTARY POTASSIUM TO PATIENTS TAKING CHLOROTHIAZIDE

INDICATIONS

1 Serum potassium values of less than 3 5 mEq per liter before treatment
2 Serum potassium values of less than 3 0 mEq per liter during treatment
3 Concurrent treatment with digitalis
4 Congestive heart failure with edema
5 Inadequate intake or excessive losses of potassium
   a Chronic renal insufficiency (some cases)
   b Acute febrile illnesses
   c Vomiting or diarrhea or both
   d Postoperative states
   e Chronic debilitating illnesses
6 Lack of ready access to medical supervision or inability to obtain levels of serum potassium regularly

SUGGESTED DOSES

Potassium chloride 2 0 gm three times a day
or
potassium triplex 8 cc three times a day

Patients who are receiving digitalis in addition to chlorothiazide should be given supplements of potassium routinely since hypokalemia exaggerates digitalis intoxication

Plan for Combination Treatment of Hypertension

Since chlorothiazide augments the hypotensive action of all of the presently available sympathetic depressant drugs and since its administration is accompanied by few unpleasant symptoms it can be profitably incorporated into the regimens of most hypertensive patients For patients who are already taking hypotensive drugs the addition of chlorothiazide usually leads to further decrease in blood pressure and frequently permits reduction of doses of other agents especially ganglion blocking drugs with correspondingly fewer side effects I should emphasize again that the dose of ganglion blocking agent must be substantially decreased *before* chlorothiazide is added to the regimen if serious hypotension is to be avoided Furthermore chlorothiazide should be given in small doses (not more than 250 mg twice daily) when it is first being added to a regimen that includes either a ganglion blocking agent or hydralazine

It is with considerable trepidation that I present a plan for treating hypertension lest I be accused of laying down stereotyped rules a grievous error in the management of hypertension for individualization of the regimen is often the secret to success Recognizing this however I think it is a good idea to have an over all plan for treatment which can be appropriately modified to suit the individual patient

Mild to Moderate Hypertension For patients with mild to moderate hypertension (groups 1 and 2)[8] who do not have any symptoms or complications treatment can be undertaken deliberately by adding one drug at a time until a satisfactory regimen is constructed (Fig 2) The blood pressure of such patients should be determined once or twice weekly but changes in dose or addition of new drugs need not be made this frequently Since

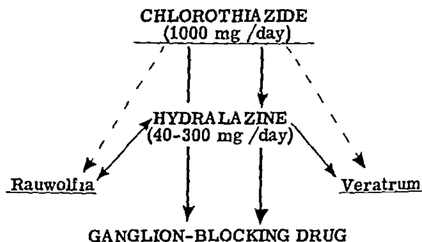


Fig 2 When hypertension is not severe the therapeutic regimen can be constructed gradually over a period of weeks When chlorothiazide alone fails to control blood pressure hydralazine can be added in gradually increasing doses This combination is so potent that in many cases it will be unnecessary to resort to other drugs Doses of hydralazine and Rauwolfia should be kept as low as possible to prevent delayed and serious side effect

chlorothiazide is well tolerated by most patients it is a good drug with which to start treatment The dose when it is being used alone in this manner is 500 mg twice daily Lower doses usually are not effective higher ones seldom increase the hypotensive effect About 30 per cent of the patients with mild to moderate hypertension and no complications will not require any additional treatment For the remaining 70 per cent or so hydralazine can be added to the chlorothiazide after two to four weeks The starting dose of hydralazine can be as little as 10 mg four times a day but it is usually 25 mg four times a day Most patients can tolerate hydralazine in this amount when it is preceded by a period of treatment with chlorothiazide Over the next four to eight weeks the dose of hydralazine is gradually increased to as much as 75 mg four times a day if needed If blood pressure is not controlled with this dosage it is usually better to add another drug

rather than risk a mesenchymal reaction by increasing the dose of hydralazine further

Sometimes the addition of small doses of a preparation of Rauwolfia are helpful at this juncture and may afford sufficient additional hypotensive effect to make the use of a ganglion blocking agent unnecessary later Rauwolfia however is a deceptive drug and the longer it is used the less one respects its hypotensive properties and the more one fears its insidious side effects Most dangerous among these are depression[9] and a parkinsonian like state both of which may be so well disguised that they escape the detection of patient family and physician alike until serious disability results

If the objective is to avoid the use of ganglion blocking drugs at all costs Veratrum can be added to the regimen instead of or in addition to Rauwolfia

When chlorothiazide hydralazine Rauwolfia and Veratrum in various combinations fail to control the hypertension adequately ganglion blocking agents should be employed The effective doses of ganglion blocking agents when used with chlorothiazide or chlorothiazide and hydralazine are often so ridiculously low that side effects are virtually absent Some physicians therefore prefer to proceed directly from hydralazine to ganglion blocking drugs without preliminary trials of the treacherous Rauwolfia or the unpredictable Veratrum

In the unlikely event that chlorothiazide is not well tolerated or is contraindicated one must resort to Rauwolfia as the starting point and from there add hydralazine and Veratrum or a ganglion blocking agent Side effects are often prohibitive when treatment is started with either hydralazine or Veratrum

If hydralazine is poorly tolerated or contraindicated Rauwolfia and Veratrum can be added to chlorothiazide in that sequence or these agents can be bypassed in favor of a ganglion blocking agent

When building a regimen in this deliberate manner by increasing the dose or adding a new agent or withdrawing an ineffective one every two or three weeks until the blood pressure is adequately controlled the physician can be confident that his patient is receiving the minimal number and minimal dosage of drugs necessary for control of the hypertension

Severe Hypertension When hypertension is severe (group 3 or group 4)[8] or cardiac or renal decompensation seems imminent indications for *treatment are more urgent* and *the situation does not* permit several weeks of manipulating drugs

Under these conditions treatment is started simultaneously or nearly simultaneously with chlorothiazide hydralazine and a ganglion blocking agent and increments in dosage are made every two or three days until the blood pressure is satisfactorily controlled (Fig 3) Then it is possible to withdraw one drug at a time to determine the minimal number and minimal dosage of drugs necessary to maintain adequate control of the hypertension

Inaugurating treatment with chlorothiazide and a ganglion blocking agent simultaneously sometimes leads to hypotensive collapse on the fourth to the sixth day when the effect of chlorothiazide becomes maximal Consequently even though reduction in blood pressure is rather urgent it is desirable to give chlorothiazide alone or in combination with hydralazine for four or five days before starting treatment with a ganglion blocking drug If administration of a ganglion blocking drug and chlorothiazide is started

simultaneously the dose of the former should be the minimal one that is permitted by tablet size and should not be increased for five or six days

CHOICE OF SYMPATHETIC DEPRESSANT DRUGS AND THEIR DOSES

Many preparations of Rauwolfia Veratrum and ganglion blocking agents are available (Table 1) It is best for the busy practitioner who understandably becomes confused by this bewildering array to become familiar with one preparation in each category and learn how to use it Tablets which contain two or more ingredients serve no useful purpose and deprive the physician of his ability to adjust the dosage precisely and to individualize regimens

Since the dangerous side effects produced by hydralazine and prepara

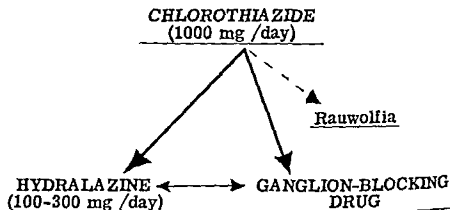


Fig 3 When hypertension is severe prompt control of the blood pressure is desirable Treatment is started simultaneously or nearly so with chlorothiazide hydralazine and a ganglion blocking drug Doses are increased more rapidly than when hypertension is not severe

tions of Rauwolfia are often insidious and delayed in onset it is wise to keep the doses of these agents as low as possible, preferably not exceeding the upper limits shown in Table 1 and maintenance doses of Rauwolfia preparations should be considerably less than the upper limits shown in Table 1 The side effects produced by ganglion blocking agents and preparations of Veratrum on the other hand are obvious and prompt and consequently the doses of these agents can be increased gradually until the desired hypotensive effect is obtained or until these side effects become intolerable At times therefore it may be possible and even advisable to exceed the upper limits of dosage for these agents shown in Table 1

SUMMARY

The concept of treating hypertension with a potent oral diuretic in combination with one or more of the sympathetic depressant drugs is a new one

This combination usually permits better control of hypertension with smaller doses of sympathetic depressant drugs and consequently produces fewer side effects A combination of hydralazine and chlorothiazide controls hyper tension for many patients and frequently obviates the need for Rauwolfia Veratrum or a ganglion blocking agent The later should be used when hydralazine and chlorothiazide fail to control the hypertension adequately but the doses required in combination with chlorothiazide are frequently so small that side effects are negligible Not infrequently administration of chlorothiazide leads to elevation of blood urea or hypokalemia or both Al though these deviations from normal are usually temporary and rarely cause symptoms periodic determinations of blood urea and serum potassium are indicated for patients taking chlorothiazide

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Diuretic Compounds in Arterial Hypertension, with Particular Reference to the Actions of Chlorothiazide, Dihydrochlorothiazide and "Steroidal Antagonists"

WILLIAM HOLLANDER, ARAM V CHOBANIAN, AND ROBERT W WILKINS

Boston University School of Medicine

In recent years a number of diuretic agents have been shown to be useful *in the treatment of arterial hypertension with or without complicating congestive heart failure*[1-6] Some of the clinical and physiologic effects of these agents are reviewed in the present study

PROCEDURE AND RESULTS

Before the development of presently available potent oral diuretic compounds it had been recognized in our laboratory for a number of years that parenteral mercurial diuretics after producing an effective diuresis frequently augmented the antihypertensive action of drugs or of sympathectomy[1] Some of our early observations of these effects of mercurial diuretics are shown in Figure 1 In addition to parenteral mercurial diuretics it also had been observed that other procedures which tended to reduce body sodium and total body fluid volume also tended to increase the antihypertensive action of drugs or of sympathectomy These procedures included acute hemorrhage chronic anemia dietary salt restriction diarrhea and dehydration Conversely it had been found that not only congestive heart failure but also other metabolic states characterized by an increase in body sodium and fluid volume operated to reduce the hypotensive action of drugs or of sympathectomy These states included steroid administration (Fig 2) and the intravenous infusion of saline solution or of blood

In view of these and other observations[6,7] a number of diuretics including chlorothiazide were given in clinical trials for the therapy of arterial hypertension Oral chlorothiazide like parenteral mercurial diuretics was found not only to enhance the responsiveness of the blood pressure to other antihypertensive drugs or to sympathectomy but also when used alone to reduce the blood pressure of hypertensive though not of normotensive subjects

During the past few months the clinical actions of a new derivative of chlorothiazide dihydrochlorothiazide* have been compared with those of

* Kindly supplied by Ciba Pharmaceutical Products Inc and also by Merck Sharp & Dohme Research Laboratories

Rx

(Dig of Leaf 0 0.2 Gm /Do throug ou tudy)

HYDRALAZINE 20mg IV

HEXAMETHONIUM 25mg V

SU 3088 mg /Day

10mg V

PENTOLINIUM mg /Day

75 mg SC

40mg IV

10mg I

BLOOD PRESSURE mm Hg

WEIGHT (Lbs)

D SPNEA

ORTHOPNEA

EDEMA

SEVERE CONGEST VE HE RT F LURE

RECO E FROM HE RT FA LURE

MARKED DIURESIS FROM MERCUH DR N HER PY

E J ♂ 40 – HCVD

TIME IN WEEKS

Fig 1 Chart showing the usefulness of mercurial diur tics in a resis ant case of hypertension with complicating congestive heart failure (Note that Su3088 is currently known as chlorisondamine or Ecolid)

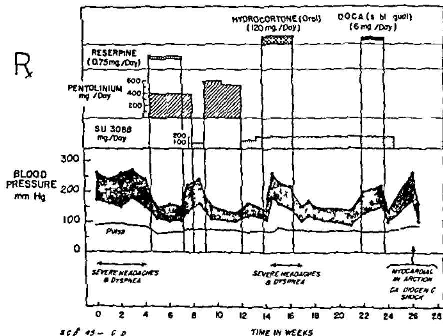


Fig 2 Chart sl owing the l locking effects of steroids on the antihypertensive action of drugs

chlorothiazide* in over 50 hypertensive subjects In Figure 3 the blood pressure responses to these thiazide compounds are compared in a hyper tensive subject Chlorothiazide alone and in combination with reserpine had no effect on the blood pressure After dihydrochlorothiazide was substituted for chlorothiazide it caused in combination with reserpine but not alone an appreciable reduction in blood pressure During initial treatment with dihydrochlorothiazide in a daily dosage of 150 mg the patient experienced extreme weakness which was associated with a marked depression of the serum potassium After reduction of the dosage of dihydrochlorothiazide to 50 mg per day the patient became asymptomatic and the serum potassium rose to within the normal range

In Figure 4 the comparative effects of chlorothiazide and dihydrochloro thiazide in another hypertensive subject with severe congestive heart failure are shown A combination of chlorothiazide ammonium chloride and mer curial diuretics produced only a slight diuresis and weight reduction which were maintained by chlorothiazide alone After dihydrochlorothiazide was substituted for chlorothiazide there was a further diuresis which was ac companied by a 20 pound weight loss a disappearance of peripheral edema and an improvement in breathing It appears unlikely that the weight gain which occurred later on during treatment was due to the development of drug resistance since the patient remained completely free of edema and continued to work for the first time in a year Of four other subjects whose congestive heart failure was resistant to chlorothiazide one responded to dihydrochlorothiazide

The comparative blood pressure effects of chlorothiazide and dihydro-chlorothiazide in a 10 to 1 dose relationship in 56 hypertensive subjects are summarized in Table 1 In a dose one tenth that of chlorothiazide dihydro chlorothiazide alone and in combination with other drugs appeared to be slightly more antihypertensive than chlorothiazide In general about one of ten subjects appeared to have a definitely greater blood pressure response to dihydrochlorothiazide than to chlorothiazide However further control observations for a longer period of time are necessary before these prelimi nary impressions can be definitely confirmed since in most of these cases dihydrochlorothiazide was directly substituted for chlorothiazide without an intervening placebo control period and in almost all cases the observations of blood pressure were recorded over a shorter period of time with dihydro chlorothiazide than with chlorothiazide

Dihydrochlorothiazide therefore on a weight for weight basis appeared to be approximately ten times more potent than chlorothiazide as a diuretic and antihypertensive agent Clinical observations as well as balance studies in two hypertensive subjects indicate that the diuretic activity of dihydro-chlorothiazide in a dose one tenth that of chlorothiazide is approximately the same as that of chlorothiazide in a group of hypertensive subjects with out heart failure The effective hypotensive dosage of dihydrochlorothiazide averaged 75 mg per day but ranged between 25 and 150 mg per day

As the dosage of dihydrochlorothiazide was increased toward a maximal dose of 150 mg per day its hypotensive action in two of seven subjects in creased, while its side effects including depression of serum potassium and rise in blood urea nitrogen were more severe and frequent

* Kindly supplied by Merck Sharp & Dohme Research Laboratories

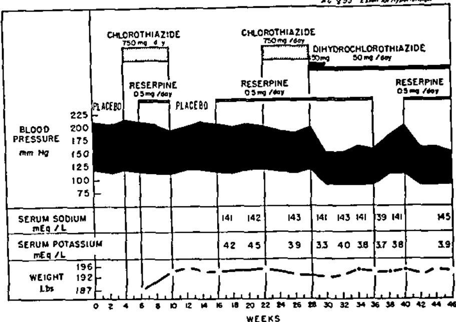


Fig 3 Chart showing the comparative effects of chlorothiazide and dihydrochlorothiazide on the blood pressure serum electrolytes and weight in a hypertensive subject

SALT ESTR CT ON
UNRESTR CTED SALT INTAKE
ADDED PO SS UM
NH_4Cl 8 gm
D G TALIS LEAF 0 2 Gm /D y
CHLOROTHIAZ DE
750 mg Day
D H DROCHLOROT AZIDE
BLOOD PRESSURE mm. Hg
175
125
90
WEIGHT lbs
242
225
209

SERUM Na mEq /L	140	14	143	143	141	145	144			146	144		138	14	140		
SERUM K mEq /L	38	53	45	37	41	38	35			41	32		37	43	36		
SERUM CO_2 CONTE vol %	36		34	37	30	35	35				34		32				
SERUM Cl mEq /L	94		94	96	94	97	98				102		97				
B U N mg %	25		23	24	27	30	28				21		17				
EDEMA					0	0	0	0	0		0	0	0	0	0		
DYSPNEA																	

0 2 4 6 8 10 12 14 16 18 20 22
WEEKS

Fig 4 Chart showing the comparative effects of chlorothiazide and dihydrochlorothiazide on the blood pressure weight blood chemistry and symptoms in a hypertensive subject with complicating congestive heart failure

TABLE 1

COMPARATIVE EFFECTS OF CHLOROTHIAZIDE & DIHYDROCHLOROTHIAZIDE ON THE BLOOD PRESSURE OF 56 HYPERTENSIVE SUBJECTS

Drugs	No of Cases	No of Responders (BP ↓ > 14/9)	Ave age B P Reduction (mm Hg)	Range of B P Red ct o (mm Hg)	A erage D ret c Dosage (mg /day)	D uret c Dose Range (mg /day)
CHLOROTHIAZIDE alone	16	7	18/10	20/10 60/25	750	375 1000
DIHYDROCHLORO alone	16	9	24/14	20/10 70/30	75	375 100
Rauwolf a ± Hydralaz ne						
+ CHLOROTHIAZIDE	32	20	30/16	20/15 60/25	750	375 1000
+ DIHYDROCHLORO	32	23	37/20	20/15 70/30	75	37 5 100
Gangl on Blocker + Rauwolf a						
+ CHLOROTHIAZIDE	8	5	.4/16	20/10 80/30	375	375 - 750
+ DIHYDROCHLORO	8	6	40/21	20/10 80/40	37 5	37 5 75

The symptomatic side effects produced by chlorothiazide and dihydro chlorothiazide were comparable (but uncommon) and included weakness epigastric distress constipation reduced libido paresthesia and skin rash As shown in Table 2 the effects of dihydrochlorothiazide on the blood chem istry also were not significantly different from those of chlorothiazide in these 25 hypertensive subjects

TABLE 2

COMPARATIVE EFFECTS OF CHLOROTHIAZIDE & DIHYDROCHLOROTHIAZIDE ON THE BLOOD CHEMISTRIES OF 25 HYPERTENSIVE SUBJECTS

SERUM Na (mEq /L)

	Cont ol	CHLORO	DIHYDRO
AVERAGE	142	141	141
RANGE	138 148	137 146	134 144

SERUM K (mEq /L)

	Cont ol	CHLORO	DIHYDRO
AVERAGE	4 2	3 7	3 7
RANGE	3 8 4 8	2 7 4 5	2 3 4 7

SERUM CO_2 Content (Vols %)

	Co trol	CHLORO	DIHYDRO
AVERAGE	28 5	30 7	30 9
RANGE	25 32	25 35	27 36

SERUM Cl (mEq /L)

	Cont ol	CHLORO	DIHYDRO
AVERAGE	103	100	99
RANGE	99 108	95 104	94 105

BUN (mg %)

	Co t ol	CHLORO	DIHYDRO
AVERAGE	20	23	23
RANGE	13 34	9 37	12 37

* *AV DOSE 750 mg /day (range 250 1000 mg /day)*

** *AV DOSE 75 mg /day (range 25 100 mg /day)*

The most frequent and striking change in the blood chemistry produced by these compounds was a reduction in serum potassium The serum potassium fell by more than 0 4 mEq /L in 40 per cent of the subjects and to below 3 5 mEq /L the lower range of normal in 24 per cent of the cases Hypochloremic alkalosis with an increase in the serum carbon dioxide content and a reduction in serum chloride was infrequent as compared with a reduction in serum potassium but it occurred in two subjects during treatment both with chlorothiazide and with dihydrochlorothiazide A decrease in serum sodium of greater than 8 mEq /L accompanied by a reduction in serum chloride occurred in one of the subjects

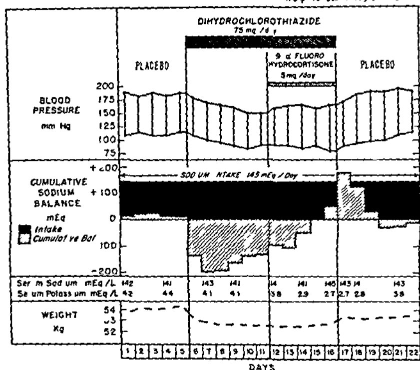


Fig 5 Chart showing the effects of fluorohydrocortisone on the hypotensive and diuretic actions of dihydrochlorothiazide in a hypertensive subject

The thiazide derivatives also caused a slight increase in the average blood urea nitrogen In two subjects the blood urea nitrogen increased during treatment by 10 mg per cent and 13 mg per cent respectively These changes in the urea nitrogen like those in the serum electrolytes usually were not clinically detectable and reverted to control values on withdrawal of the drugs

An analysis of a larger series of cases treated with chlorothiazide indicates that some of the conditions which predispose to alterations in the blood chemistry include an excessive drug dosage pre-existing renal disease and a restricted dietary intake of salt In view of these observations chlorothiazide and dihydrochlorothiazide are now given in as reduced a dose as possible and usually with a diet unrestricted in sodium and high in potassium

The mode of action of dihydrochlorothiazide on the blood pressure appears to be similar to that of chlorothiazide Dihydrochlorothiazide as has been previously reported with chlorothiazide[1 4 8] is capable of reducing the blood pressure without an accompanying reduction in body sodium As shown in Figure 5 dihydrochlorothiazide continued to exert an antihypertensive action even when fluorohydrocortisone had counteracted the natriuretic effect of dihydrochlorothiazide and had restored the sodium balance to and above control values The slight rise in blood pressure though not to pretreatment levels during the repletion of body sodium by fluorohydrocortisone suggests that a reduction in body sodium tends to enhance the antihypertensive action of dihydrochlorothiazide Previous studies indicate that a reduced body sodium not only may augment but also may maintain the hypotensive action of chlorothiazide[1 4]

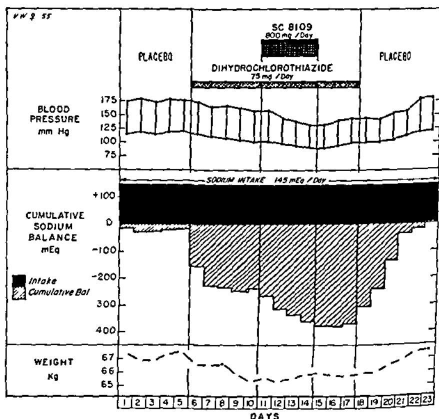


Fig 6 Chart showing the effects of a steroidal antagonist SC8109 on the hypotensive and diuretic actions of dihydrochlorothiazide in a hypertensive subject

Because of the possibility that an increased excretion of aldosterone might account for the absence of sodium depletion during continued chlorothiazide treatment, the effects of SC8109* a steroidal antagonist[9 10] were studied on the actions of dihydrochlorothiazide[8] The results in Figure 6 are similar to those previously reported with chlorothiazide In the experi

Chemically identified as 3 (3 oxo 17β hydroxy 19 hor-4 androsten 17α yl) and supplied by G D Searle & Co

TABLE 3 THE EFFECTS OF SC8109 AND SC6594 ON THE BLOOD PRESSURE AND SODIUM BALANCE IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

SUBJECT									
AGE	SEX	DIAGNOSIS	DRUG	ROUTE	DOSAGE (mg/Day)	DURATION (Days)	DIETARY SODIUM INTAKE (mEq/Day)	NET BALANCE OF SODIUM (mEq)	CHANGE IN BLOOD PRESSURE (mm Hg)
F M 43	M	Essential Hypertension	SC8109	I M	300	5	94	−113	+ 5/− 5
E W 48	F	Essential Hypertension	SC8109	I M	300	3	9	− 99	−10/+ 5
R D 45	F	Essential Hypertension	SC8109	Oral	750	4	179	−216	− 5/+ 5
			SC8109	Oral	750	4	77	−197	−20/−10
			SC8109	Oral	750	4	77	−181	−35/−10
V W 55	F	Essential Hypertension	SC8109	Oral	800	4	145	−114	−20/−10
R C 49	M	Conn's Syndrome	SC8109	I M	300	5	77	−194	+ 5/+ 5
M G 39	F	Post Steroid Hypertension	SC6594	I M	450	5	9	−195	0/− 5
E E 25	F	Normal	SC8109	Oral	750	3	145	−145	− 5/ 0
			SC6584	I M	450	2	145	− 42	
I G 27	M	Normal	SC8109	Oral	750	3	145	− 80	+ 5/ 0
			SC6594	I M	450	2	145	− 43	0/ 0
A T 28	M	Normal	SC8109	Oral	750	4	145	−278	− 5/− 5
			SC8109	Oral	750	2	145	−169	0/− 5

Added to chlorothiazide
Added to hydrochlorothiazide

ment shown in Figure 6 SC8109 was added to dihydrochlorothiazide on the eleventh metabolic day during a daily intake of 145 mEq of sodium At this time the net loss of sodium was 125 mEq and no further reductions in body sodium and blood pressure were being produced by the dihydrochlorothiazide SC8109 then given for four days in combination with dihydrochlorothiazide produced an additional loss of 114 mEq of sodium and a decrease in blood pressure of 20/10 mm Hg These as well as the previous observations with chlorothiazide [8] support the idea that an increase in aldosterone activity may occur during the administration of the thiazide compounds and tends to counteract the natriuretic and possibly some of the hypotensive

	Duration	B P	Wgt (kg)	Body Na /Kg Wgt	Serum (mEq /L) K	Na	CO_2	Cl
Control	4 Wks	180/95	89 8	32 5	4 9	147	26	105
Early Rx	1 Week	145/95	88 0	30 2	3 5	147	26	105
Late Rx	8 Wks	150/90	89 3	32 7	3 6	145	28	102

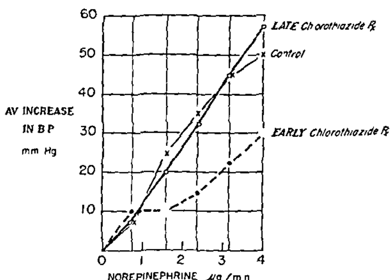


Fig 7 Chart showing the early and late effects of chlorothiazide on the blood pressure responses to norepinephrine

effects of these agents However these findings do not exclude a nonspecific effect of SC8109 on salt excretion and blood pressure especially since SC8109 alone causes a sodium diuresis in normal and in hypertensive subjects during a normal intake of dietary sodium (Table 3)

SC8109 and another steroid SC6584 * have been tested in 11 subjects but only for two to seven days because of a limited supply of the drugs The effects of these compounds on the blood pressure and sodium balance of nine of the 11 subjects are summarized in Table 3 SC8109 given alone to three subjects with essential hypertension and one subject with primary hyperaldosteronism had no discernible effect on the blood pressure although

* Chemically identified as 17α propyl-4 5β dihydro-19 nortestosterone and supplied by G D Searle & Co

it caused a sodium diuresis of 80 to 278 mEq In one of the subjects (R D) who was restudied during a restricted sodium intake SC8109 appeared to exert a hypotensive effect It is noteworthy that the net loss of sodium at this time was no greater than that caused by SC8109 during a dietary sodium intake of 179 mEq SC8109 in combination with chlorothiazide or dihydrochlorothiazide produced a further reduction of blood pressure in two of four hypertensive subjects ranging from 20/10 mm Hg to 35/10 mm Hg In both of these subjects R D and V W the hypotensive effect of SC8109 was associated with further losses of body sodium SC8109 alone had no effect on the blood pressure of three normal individuals although it caused a sodium diuresis of 80 to 278 mEq SC6584 given alone to two normal subjects and one patient with hypertension following steroid treatment of psoriasis appeared to increase sodium excretion without altering the blood pressure

In view of the apparent selective hypotensive action of chlorothiazide in arterial hypertension it has been postulated that the compound might lower blood pressure by interfering with some pressor mechanism Although preliminary observations have suggested that chlorothiazide might depress serum renin subsequent studies have not substantiated these findings[4] The experiments shown in Figure 7 also indicate that the hypotensive effect of prolonged chlorothiazide treatment is not necessarily due to an alteration in the reactivity of the blood pressure to norepinephrine However they do suggest that the initial reduction in blood pressure caused by chlorothiazide treatment might involve some different mechanisms than that seen later on In Figure 7 the increases in blood pressure caused by increasing doses of norepinephrine after one week of chlorothiazide treatment were considerably less than those caused by norepinephrine in the control period However after more prolonged chlorothiazide treatment (eight weeks) the blood pressure even though still reduced became as responsive to norepinephrine as it had been in the control period Similar types of blood pressure responses were obtained in three of five experiments and appeared to parallel the changes of body sodium rather than any of the other electrolyte measurements made

SUMMARY AND CONCLUSIONS

Chlorothiazide and mercurial diuretics appear to have a "selective" antihypertensive effect in arterial hypertension in the sense that they have no demonstrable hypotensive action in normal individuals These findings suggest that these two agents may operate similarly against some arterial pressor mechanism Sodium depletion as indicated by laboratory studies appears not to be the sole or even the main cause of the antihypertensive action of chlorothiazide or dihydrochlorothiazide although it may maintain and augment the hypotensive action of these compounds The absence of sodium depletion following prolonged chlorothiazide or dihydrochlorothiazide treatment may be due to an increase in aldosterone activity

Dihydrochlorothiazide in one tenth the dose (by weight) of chlorothiazide appears to be slightly more effective than chlorothiazide as an antihypertensive agent It also appears to be a more effective diuretic than chlorothiazide in congestive heart failure However longer term studies with adequate controls are necessary to establish the validity of these preliminary observations

SC8109 a steroidal antagonist not only augments the diuretic effects of chlorothiazide and dihydrochlorothiazide but also is capable of enhancing the hypotensive action of these compounds When used alone SC8109 also has a potent diuretic action Short term studies with SC8109 suggest that steroidal lactones deserve further clinical trials in the treatment of hypertension and of congestive heart failure

ACKNOWLEDGMENT

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The Exact Role of Chlorothiazide Used Alone and in Combined Drug Therapy of Hypertension

S W HOOBLER JOHN M WELLER AND PEDRO BLAQUIER
University of Michigan Medical School

It is very difficult to present any explanation of the "exact role of chlorothiazide (Diuril) both because our studies of this very unusual drug are incomplete and because the observations of some investigators have led to conflicting interpretations Consequently this presentation will deal with the clinical use of chlorothiazide and the evaluation of theories concerning its mode of action when used in combination with ganglion blocking agents and when given as the sole antihypertensive drug

EFFECT OF CHLOROTHIAZIDE IN THE PRESENCE OF REDUCED SYMPATHETIC VASOMOTOR TONE

It is abundantly evident that a maintenance dose of chlorothiazide (0 5 gm twice daily) will reduce the requirement of any autonomic blocking agent by at least 50 per cent[1] For this reason chlorothiazide is useful as background medication when ganglion blocking agents are prescribed It is perhaps less well recognized that the depressor effect of chlorothiazide *is enhanced by a long previous supradiaphragmatic sympathectomy*[2] Table 1 demonstrates the effect of the drug on the blood pressure in some sympathectomized patients It will be seen that orthostatic normotension was usually achieved with little or no requirement for the additional use of a ganglion blocking agent The dividend in terms of continuous asymptomatic blood pressure control is clearly evident We wish that more patients especially the younger and more severely ill would select this approach to treatment The beneficial effect which sympathectomy confers on the chlorothiazide response has persisted up to ten years

The synergism between chlorothiazide administration and reduced sympathetic vasomotor activity is thus apparent The hemodynamic explanation is not clear but it would seem possible to develop a theoretical explanation on the basis of the following observations Ganglion blocking agents lower blood pressure by reducing cardiac output[4] after blockade the arterial pressure falls markedly when the circulating blood volume is reduced[5] Wilson and Freis have furthermore demonstrated a maintained reduction of plasma volume during treatment with chlorothiazide[6] The synergistic effects of ganglion blockade and chlorothiazide would seem to result from the inability of the reduced sympathetic tone to assure a normal cardiac output in the presence of a depleted plasma volume

TABLE 1 CHLOROTHIAZIDE IN POST SPLANCHNICECTOMY HYPERTENSION

Recent Sympathectomy

BP mm Hg	I	II Hu Ri	III	I	II Ro Po	III	I	II Bo Cl	III	I	II Ro Ca	III	I	II E Gi	III
Recumbent	198/140	210/138	160/108	240/150	250/156	180/130	202/132	230/148	157/102	269/166	227/142	208/140	206/135	200/129	144/108
Standing	192/146	196/142		240/150	160/136	130/100	168/128	210/150	140/112	284/192			220/160	190/118	144/106
Home reading (Diurnl)		—			—		S 137/96	—		S 139/110	—	R 150/117	S 144/106	—	R 142/94
Postop interval (months)		6			7			9			9½			10	

Long standing Sympathectomy

BP mm Hg	I	II Jo Gu	III	I	II Ev La	III	I	II Ma Po	III	I	II No Tr	III	I	II El Re	III
Recumbent	240/150	252/155	210/120	210/120	242/151	130/88	220/144	210/120	182/112	240/140	210/123	182/98	196/134	179/119	230/144
Standing		248/155	142/108	152/104	173/116	142/90		180/120	164/120			162/100	200/134		210/140
Home reading (Diurnl)	S 135/91	—	R 162/98	S 130/94	—	R 154/96		—	R 160/110	S 164/95	—		S 114/78	—	R 134/94
Postop interval (months)		34½			41½			79			82			119	

Readings Home = Average of five blood pressures prior to last clinic visit Other readings were clinic casual blood pressures S = Standing R = Recumbent I = Preoperative II = Postoperative blood pressure prior to beginning chlorothiazide III = Latest blood pressure on varying periods of chlorothiazide treatment Operation was supradiaphragmatic splanchnicectomy Note effect of chlorothiazide in reducing recumbent and standing blood pressure regardless of length of postoperative interval
Jo G and El Re ec ed Inve n 15 mg and 30 mg r pecti ely in add t n to Hlo otl a ide

EFFECT OF CHLOROTHIAZIDE AS THE SOLE ANTIHYPERTENSIVE AGENT

It is more difficult to demonstrate conclusively that the blood pressure is reduced when chlorothiazide alone is administered. We believe that this effect is more frequently observed in the milder forms of hypertension, that it depends on an adequate dosage (0.5 gm two to three times daily over a period of one to two months) and that it is more readily produced if the intake of sodium is restricted to 800 mg per day or less. Our previously reported experience[3] as well as that illustrated in Figure 1 demonstrates the undoubted effect of such a regimen in some cases. If adequate potassium intake is assured, little difficulty is encountered in prolonged treatment except in the occasional individual who exhibits drug intolerance. In some cases in which the sodium intake is severely restricted the hypotensive effect may persist for a considerable time after withdrawal of chlorothiazide.

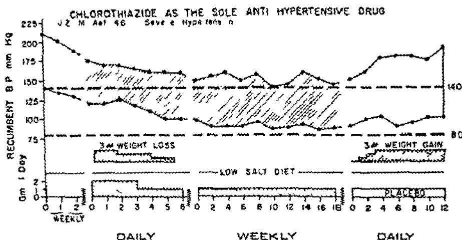


Fig. 1. Effect of chlorothiazide on the blood pressure in severe essential hypertension.

The explanation for the effect of chlorothiazide when used as the sole antihypertensive drug is under current investigation in our laboratory. The following preliminary observations have been made: (1) Change in weight does not necessarily parallel antihypertensive effect. (2) A largely orthostatic reduction in blood pressure is not a prominent feature. (3) The antihypertensive effect can be prevented or abolished by the addition of sodium chloride to the diet but not by addition of potassium salts. Finally, (4) cardiac output is not reduced. In some cases at least, treatment with chlorothiazide has lowered total peripheral vascular resistance.* If one accepts the findings of Hollander, Chobanian and Wilkins[7] that total body sodium and extracellular fluid volume are not chronically depleted or that if they are reduced[8] there is no parallel effect on the blood pressure, we are left in complete ignorance concerning the mode of action of chlorothiazide. We remain as uncertain as the investigators who attempted unsuccessfully to define the mechanism by which a low sodium diet reduced the blood pres-

* We are indebted to Dr. James Conway, who has to date made such observations in four patients.

sure It is probable that the modus operandi is similar Fortunately chlorothiazide provides us with an easier and more effective means than diet for achieving sodium chloride depletion

It is to be hoped that with this new drug fundamental studies on the role of sodium in hypertension may be performed Certain possibilities deserve further exploration Are there internal rearrangements of sodium between cells and extracellular fluid which may reduce vascular tone? Does chlorothiazide interfere with the renal pressor mechanism? Is interstitial fluid pressure a factor in maintaining arteriolar and capillary vascular resistance? Does the drug alter vascular reactivity to circulating humoral substances which are responsible for maintaining vascular tone? Does the drug possess in addition to a diuretic action some central or peripheral sympathic inhibitory effect as is suggested by the not infrequent appearance of impotence during therapy? Whatever may be the final answer to these fundamental questions there is little doubt that the advent of chlorothiazide opens new horizons for the investigation and treatment of hypertension

SUMMARY AND CONCLUSIONS

Chlorothiazide has a synergistic action with ganglion blocking agents or sympathectomy in lowering the blood pressure in hypertension Severely hypertensive subjects who have undergone a previously unsuccessful sympathectomy are often rendered normotensive by the administration of chlorothiazide In association with a low salt intake the drug not infrequently lowers the blood pressure of hypertensive patients Hypotheses concerning its possible mode of action are discussed

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Combined Drug Therapy of Hypertension—Sympathetic Depressants and Diuretics Managing Side Effects of Treatment

RALPH V FORD

Baylor University College of Medicine

BASIC CONSIDERATIONS

When using compounds such as the sympathetic depressants and diuretics in the treatment of hypertension the therapist should be acquainted with the best method of administration and the possible untoward reactions that might be encountered Undesirable side effects of the newer drugs can become a serious problem but they are usually predictable The incidence of their occurrence can be reduced or frequently prevented if the drugs are handled skillfully

When potent therapeutic agents are used a few important generalizations are applicable (1) A drug should be used only when indicated and then it should be used in adequate amounts Otherwise the patient is exposed to potential untoward reactions without benefit of therapeutic value (2) Especially in the treatment of hypertension with sympathetic depressants and diuretics the dose of each drug should be titrated" In other words the dose of the drug has to be adapted to the requirements of the patient There is no such thing as an average dose

MANAGING THE SIDE EFFECTS OF DIURETICS

Diuretic agents that can be administered orally for long periods of time may have value in the adjunctive therapy of hypertension We have shown that the antihypertensive potency of a diuretic is proportional to its potency as a natriuretic agent[1] Currently the only orally active diuretic with significant value in the treatment of hypertension is chlorothiazide (Diuril)

The principal side reactions associated with its use are those attributable to all potent diuretic agents namely gastrointestinal upsets and biochemical dysequilibria Hypochloremic alkalosis the most common example of the latter can be avoided or corrected by the concurrent use of ammonium chloride (4 to 8 gm daily) or by liberalizing the salt content of the diet Significant hypokalemia has only rarely been seen and this only in patients who were not eating satisfactorily or who continued to receive the drug after diuresis was no longer experienced (due to serious metabolic imbalances) When used concurrently with other antihypertensive agents it will be possible frequently to reduce the dose of the latter thereby reducing their untoward side effects

MANAGING THE SIDE EFFECTS OF SYMPATHETIC DEPRESSANTS

Rauwolfia The most frequent side effect of Rauwolfia therapy is nasal congestion Though this is nearly as common after long periods of therapy as in the early stages most patients report that it becomes less severe with prolonged administration Vasoconstrictor nose drops may be helpful Antihistamines have not been of value

Most of the patients note some increase in the frequency of bowel movements but in most cases this is temporary and not sufficiently severe to be called diarrhea Mild dizziness occurs in 10 to 20 per cent of patients during the first month of therapy This is not postural and is not necessarily related to a fall in blood pressure Excessive sedation weakness and fatigue are seen with some regularity but these complaints all tend to decrease as therapy is continued Although tolerance to the side effects develops tolerance to the antihypertensive effects of Rauwolfia preparations does not seem to be a clinical problem

Probably the most serious side effect of the Rauwolfia compounds is the agitated depression that is occasionally observed The manifestations can be insidious and may so closely resemble the anxiety manifestations frequently associated with hypertension that the physician may not recognize them as part of an unfavorable reaction to the drug Nevertheless they can be sufficiently serious that suicide is a distinct possibility If mood elevating drugs such as dextroamphetamine are not helpful, the Rauwolfia should be discontinued

Ganglionic Blocking Agents There is little difference in the side effects due to the various ganglionic blocking agents In general ganglionic blockade is autonomic ganglionic blockade and the majority of the side effects are due to blockade of the parasympathetic ganglia However in some patients excessive blockade of the sympathetic ganglia may result in dizziness and syncope due to excessive reduction in blood pressure Patients soon learn to get out of bed slowly and avoid quiet standing There are many considerations to be kept in mind when using the ganglionic blocking agents One of the things to be carefully guarded against is excessive reduction of blood pressure in the patient who already has serious renal vascular damage Here we have the peculiar paradox of the patient who has renal vascular damage and progressive disease due to hypertension If we reduce his blood pressure too drastically then we merely aggravate the renal decompensation However if effective reduction in blood pressure can be obtained without aggravating the renal decompensation anatomic damage to the kidney usually can be arrested

The acute response to a ganglionic blocking agent is characterized by a rather sharp reduction in glomerular filtration rate and renal plasma flow but hemodynamic readjustment takes place and these functions return to normal if the blood pressure is not reduced excessively

If the blood pressure is reduced excessively it is important to keep in mind that renal function is less in the standing position Should excessive reduction in blood pressure occur it is best to have the patient remain supine Excessive reduction in blood pressure is easily corrected by merely administering a vasopressor agent and raising the blood pressure to high normotensive or low hypertensive levels

How far then can the blood pressure be reduced in the patient with

TABLE 1 DEGREE OF BLOOD PRESSURE REDUCTION (UPRIGHT) DEPENDENT ON AMOUNT OF RENAL DAMAGE

BLOOD UREA NITROGEN (mg/100 cc)	REDUCE UPRIGHT BLOOD PRESSURE TO
Normal	130–150/80–100
30 to 60	150–170/100–110
60 to 100	180–190/110–120
100	No reduction

Do not reduce blood pressure further if blood urea nitrogen level rises

renal disease? A suggested approach to this problem is presented in Table 1 Although this is a rough estimate as to the degree of blood pressure reduction close attention must be paid to this determination As the blood pressure is progressively reduced the blood urea nitrogen tends to become elevated at any point one should maintain the blood pressure at this level or slightly higher

One of the most troublesome complications with the use of the ganglionic blocking agents is constipation due to blockade of the parasympathetics If not handled quickly this can lead to ileus and complete paralysis of the bowel When this occurs it should not be confused with bowel obstruction In Figure 1 is presented a patient who was allowed to develop ileus This should never occur if the constipation is treated early and effectively Certainly in this case "an ounce of prevention is worth a pound of cure" Suggestions for preventing this problem are (1) Prostigmin in a dose of 15 to 30 mg orally or (2) milk of magnesia in a dose of 15 to 30 cc or Cascara sagrada in a dose of 10 to 15 cc If these are inadequate then 30 cc of milk



Fig. 1 A Roentgenogram taken in the supine position There is marked distention of both the large and small bowel due to ileus B In the upright position multiple fluid levels are evident throughout the bowel (due to ileus) (From Moyer Ford et al A.M.A. Arch Int Med 98 387 1956)

of magnesia and 15 cc of Cascara sagrada should be given concurrently As stated before if constipation is treated early and effectively ileus should never occur Should ileus occur however the patient should be given 1 mg of Prostigmin every hour until the ileus is relieved

The most important consideration in using ganglionic blocking agents is individualization of dose It is obvious that an average dose would be ineffective in some patients and intolerable in many others Therefore it is necessary to start out with a small dose and gradually increase the dose until the effective level has been obtained for each patient

Usually the ganglionic blocking agent is more effective initially than it is after a week or two This is a phase of partial tolerance The Rauwolfia compound is used concurrently since it makes the blood pressure reduction of the ganglionic blocking agent more stable The concurrent use of a diuretic such as chlorothiazide and a Rauwolfia compound reduces the required dose

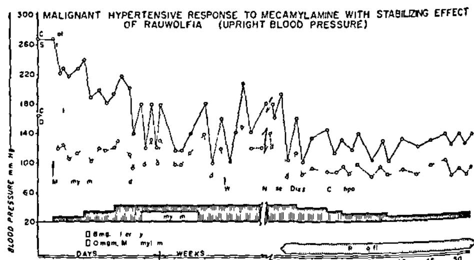


Fig 2 The stabilizing effect of Rauwolfia on ganglionic blockade (From Moyer Ford *et al* A M A Arch Int Med 98 187 1956)

of the ganglionic blocking agent and therefore decreases the side reactions due to parasympathetic blockade This effect is no doubt due to the depressant effect of Rauwolfia in the sympathetic nervous system and the brain The supportive effect of the ganglionic blocking agent further depresses the outflow of vasoconstrictor impulses over the sympathetic nervous system

Also it must be remembered that the dose of the ganglionic blocking agent is a fixed amount just as in the use of a fixed amount of insulin in the treatment of diabetes Therefore if the patient is subjected to excessive stress he will tend to break through the ganglionic blockade and his blood pressure will rise It is frequently necessary to readjust the dose of the blocking agent during periods of stress as well as during periods of relaxation During the latter the patient often will experience excessive reduction in blood pressure due to the decreased requirement of the ganglionic blocking agent resulting from decreased outflow of vasoconstrictor impulses Therefore these patients who are receiving ganglionic blocking agents must be kept under constant supervision

Occasionally the question arises as to whether the Rauwolfia actually has any effect on the blood pressure response to the more potent ganglionic blocking agent In Figure 2 is presented a patient who was treated with a ganglionic blocking agent His blood pressure was very erratic After the Rauwolfia was added a typical response was observed The variability of the blood pressure decreased and the dose requirement of the ganglionic blocking agent decreased

Other more rare side effects of an adverse nature have been described with these agents but fortunately they usually disappear on discontinuation or reduction of the dose of the drug

COMBINED EFFECTS OF AN ADVERSE NATURE AND THEIR MANAGEMENT

In this era of polypharmacy it sometimes becomes difficult to establish the precise origin of an untoward side effect However full knowledge of the specific pharmacologic attributes of each chemotherapeutic agent employed will clarify the situation These have been dealt with on an individual basis in the foregoing discussion with one exception This exception is the rather pronounced augmentation of the antihypertensive properties and its contemporaneous side effects of the ganglionic blocking agents by diuretics especially chlorothiazide This demands that the dose of the ganglionic blocking agent be reduced This feature is merely another reflection of the necessity for individualization in dosage for the specific patient

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Effect of Drug Therapy on the Prognosis of Patients with Hypertension

CHARLES HEIDER

Baylor University College of Medicine

Since reduction of blood pressure in patients with hypertension can be readily accomplished by the use of recently developed drugs it has become important to evaluate the effect of this drug therapy on the prognosis of patients with this disease Some practitioners still question whether *or not* beneficial effects are derived from blood pressure reduction in these patients and choose not to treat the disease at least not with the newer and more effective drugs That hypertension results in damage to such vital organs

as the brain heart and kidney has been well established For example direct evidence from tissue biopsy and indirect evidence from functional capacity tests indicate that all degrees of renal damage occur in patients with this disease[1 6]

Over a six year period we have accumulated vital data on a series of 133 hypertensive patients in whom renal functional clearance tests had been performed Analysis of these data revealed that variable degrees of renal heart and central nervous system damage already existed in approximately 75 per cent of these patients at the time they first presented themselves for treatment[7] Using this selected group of patients we attempted to analyze their outcome over the six year period with respect to improvement control or progression of the disease as well as mortality When the data were summarized several correlations were found and they are presented in this report as evidence of the effect of drug therapy on prognosis in this disease

METHODS

The patients used in this series were selected at random from the large outpatient hypertensive clinic services of a city county charity hospital and a Veterans Administration hospital and were accumulated over a six year period All patients had sustained blood pressure elevations above 150/100 mm Hg during a control observation period of three to four weeks During the control period routine laboratory examination blood urea nitrogen determinations electrocardiograms and chest x rays were obtained In addition standard renal clearance tests were performed to obtain the glomerular filtration rate (inulin clearance) and the renal plasma flow (para aminohippurate clearance)

Following the control period the patients were started on antihypertensive drug therapy usually consisting of a ganglionic blocking agent in combination with a Rauwolfia compound Dosages of drugs were regulated so as to maintain effective blood pressure reduction without producing serious side effects Serial chest x rays electrocardiograms and routine laboratory examinations were repeated at three to four month intervals in patients who continued their follow up visits to the clinics

RESULTS

After a six year period an attempt was made to establish the existing status of this group of patients We were able to account for 116 of the original 133 patients The whereabouts of the other seventeen could not be ascertained Further analysis revealed that only 62 of these 116 patients had received adequate therapy on the basis of blood pressure reduction and consistent drug therapy Fifty four of the patients had not received adequate treatment either because they had moved from the area and did not continue therapy or had voluntarily discontinued their medications before an effective program was established Since the two groups were comparable with regard to number and original selection this gave us the opportunity to compare the prognosis in both treated and untreated patients In 64 of the patients follow up renal clearance studies and cardiac evaluations were performed Nineteen of these patients had not been treated The follow up periods varied from one to six years

TABLE 1 PROGNOSIS OF HYPERTENSIVE PATIENTS BASED ON GLOMERULAR FILTRATION RATE

AVERAGE MBP (mm Hg)	GLOMERULAR FILTRATION RATE (cc /min.)	NO OF PATIENTS		MORTALITY			
		TREATED	UNTREATED	TREATED		UNTREATED	
				No	%	No	%
152	>100	19	14	2	10	5	36
157	80–99	15	9	2	13	3	33
168	60–79	16	12	3	19	6	50
169	40–59	5	10	1	20	10	100
168	<40	7	9	3	43	9	100
Total		62	54	11	18	33	61

The prognosis in treated and untreated hypertensive patients is shown in Table 1. The over all mortality in patients treated was 18 per cent compared to 61 per cent in untreated patients. When divided into subgroups on the basis of the initial glomerular filtration rate the data indicate that mortality increases and the prognosis becomes worse if renal damage exists. Evidence of renal damage correlated well with the electrocardiographic and funduscopic findings of hypertensive vascular disease indicating the progressive generalized course of the disease. This is true for both treated and untreated patients. However mortality was higher in untreated patients in each group and was 100 per cent in those with initial filtration rates below 60 cc /minute. These patients also were found to have a greater degree of hypertension as shown by mean blood pressures of around 168 mm Hg. *On this basis untreated patients with hypertension tend to run a continuous* downhill course resulting in further renal and myocardial impairment and ultimately death.

Data shown in Table 2 will help to point out how therapy affected the course of this disease. Untreated patients showed a continuous decline in renal function, a persistent blood pressure elevation and no improvement in electrocardiographic changes or x ray evidence of cardiac enlargement. Conversely treated patients showed a marked reduction in blood pressure without changes in renal function and approximately 30 per cent had improvement in the electrocardiograms and decreased cardiac size by x ray. Since it was not possible to establish with accuracy the duration of the disease in most of the patients no conclusions could be drawn as to how

TABLE 2 FOLLOW UP STATUS IN TREATED AND UNTREATED HYPERTENSIVE PATIENTS

	TREATED		UNTREATED	
No of Patients	45		19	
	C	F	C	F
Blood urea nitrogen (mg %)	24	26	23	61
Glomerular filtration rate (cc /min)	81	76	84	64
Renal blood flow (cc /min)	745	711	782	546
Mean blood pressure (mm Hg)	167	118	165	170
Improved electrocardiogram (%)		29		0
Improved x ray (%)		30		5
Duration of follow up (mos)		27		26

C = Control values
F = Follow up values

long it takes this disease to reach the final stages if untreated Undoubtedly many patients had had their disease for a long time and many practitioners have had patients whom they have followed for years untreated without apparent ill effects Conversely in its malignant form it runs an accelerated course One finding of interest however is that the reduction in renal function in untreated patients occurred over an average follow up period of 26 months (see Table 2) The figures presented are averages for the group and although not shown the reduction in function is much greater in patients with diastolic pressures above 130 mm Hg Thus the changes taking place in these patients are more subtle than those which are ordinarily considered and eventually contribute to the patient s demise Evidence indicates that these changes can be arrested by reducing blood pressure with proper drug therapy and can even be improved in some cases

TABLE 3 CAUSES OF DEATH

		TREATED		UNTREATED	
CAUSE	NUMBER	No	%	No	%
Uremia	15	0	0	15	100
Cerebral vascular accident	19	9	47	10	53
Cardiac	4	0	0	4	100
CVA with uremia	3	1	33	2	67
Others	3	1	33	2	67
Survival time (mos)			22		11
Total	44	11	25	33	74

In Table 3 are listed the causes of death in the 44 patients who died Of 15 patients who died in uremia all were untreated Cerebral vascular accident as a cause of death was evenly distributed in both groups and four untreated patients died from cardiac complications

SUMMARY

A series of 133 patients with hypertensive vascular disease is presented as to their ultimate outcome over a six year period Most of the patients already had advanced disease at the time they were first seen Seventy per cent had evidence of reduced renal function which offers a poorer prognosis and which progresses if untreated further reducing life expectancy Seventy five per cent had abnormal electrocardiograms as well as chest x ray evidence of cardiac enlargement These showed slight improvement when treated and progression when untreated Mortality the most definite of all end points was greatly reduced in the treated group of patients the lives of those who died in this group were extended an average of 11 months compared to those of the untreated From these data the conclusion is drawn that hypertensive vascular disease if untreated offers a very poor prognosis that the disease should be treated vigorously and early with effective drugs and that by so doing lives will be prolonged and morbidity and mortality from the disease reduced

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Discussion

CARL F SCHMIDT *Moderator*

KARL BEYER	WILLIAM HOLLANDER
WILLIAM DAESCHNER	SIBLEY HOOBLER
HARRIET DUSTAN	JOHN HOWARD
FRANK A FINNERTY	JOHN MOYER
RALPH FORD	WILLIAM PATON
EDWARD FREIS	HENRY SCHROEDER
RAY GIFFORD	REGINALD SMITHWICK
ARTHUR GROLLMAN	ELLARD YOW
CHARLES HEIDER	

DR SCHMIDT I have a number of questions which have been given to me I shall present them to the panel for discussion Is it worth while to use anti hypertensive drugs in patients who have high systolic and normal diastolic blood pressure as in arteriosclerosis? Dr Hoobler will you answer that?

DR HOOBLER I think that people with arteriosclerotic hypertension develop sudden blood pressure elevations during which time cerebral vascular accidents occur Therefore I would like to see the blood pressure brought down if it can be done I would of course use a mild agent such as chlorothiazide in combination with Rauwolfia with careful supervision for the development of psychiatric depression This approach seems to be effective in this situation depending upon the magnitude of blood pressure elevation

DR SCHROEDER May I disagree with Dr Hoobler somewhat? The question to be answered it seems to me in treating a hypertensive is does the patient have or does the patient not have peripheral vasospasm i e increased peripheral resistance? Many patients with a normal diastolic pressure and a high systolic pressure don t have increased peripheral resistance We have

treated patients with blood pressure of 180/80 and we can get their pressure down to 140/40 but they don't like it and we don't either Patients of that sort I prefer to treat with the mildest drugs if at all and to think of the changes in diastolic pressure as being the most important thing and rather neglecting the systolic pressure

DR GROLLMAN I would like to add to Dr Schroeder's point of view and to go further by saying that if the diastolic pressure is normal as the question indicated lowering of the pressure is contraindicated and nonphysiologic If anything you will only hasten the complications because by lowering the blood pressure you are producing ischemia of the tissues and it seems to me that you would hasten myocardial infarction and other difficulties It certainly would make the patient feel badly Now it's true that in many of these patients probably as a result of the concomitant nephrosclerosis there is a rise in diastolic pressure above normal and I'd go along with Dr Hoobler and say that one should lower their blood pressure because of their increased diastolic pressure doing this very cautiously in view of the underlying arteriosclerosis

DR SCHMIDT Any other comments?

DR HOOBLER May I defend myself? I agree with these generalizations but I was thinking about the individual whose blood pressure at one moment might be 190/90 but under emotional stress would increase to 240/130 I have seen patients who soon after such an episode had a cerebral vascular accident I think this occurs frequently in these people with generalized arteriosclerosis If I could prevent the peak of the pressure in these patients I would hope that this would reduce the likelihood of a cerebral vascular accident I don't think we're hurting these people by reducing their blood pressure because they don't have coronary pain nor any other symptoms of ischemia when you cautiously lower their pressure When you can get their pressure down a little bit and safely then I think that perhaps they have more protection against vascular accidents

DR GIFFORD I think that the answer to this is that we don't know Nobody has done any follow up study to find out what happens to people with this so called arteriosclerotic hypertension with high pulse pressure either with treatment or without Unless somebody treats some of them we're not going to know what happens or whether it's beneficial I can't think that a systolic pressure of 230 mm Hg even though the diastolic is 80 is helpful When I give these patients antihypertensive drugs both levels do not come down The diastolic pressure may come down a little but the systolic pressure comes down much more thus narrowing the pulse pressure I don't think it follows that because they have a pulse pressure of 150 or 200 that it's going to be maintained at that rate if you reduce the blood pressure Actually the systolic does come down more than the diastolic which narrows their pulse pressure

DR SCHMIDT Granted that the goal of the specific reversal of the unknown etiologic factor in hypertension is not yet obtainable define what you would consider to be the best possible approach toward the ideal antihypertensive agent What should such an ideal agent do so far as cardiovascular hemodynamics are concerned? Does anybody want to summarize this?

Dr Schroeder I'll take a crack at it Dr Schmidt I would say let's have one drug which reduces vasospasm without altering blood volume without changing cardiac output without having any side effects which gently allows the blood pressure to fall in direct proportion to the amount of drug that is given and which has no immediate or late toxic reactions

Dr Paton I would like to comment on this just as a pharmacologist One is often confronted with a situation where a good many remedies are available for one disease and I'm coming to the unpleasant view that clinical trials become of major importance under these conditions Listening to the discussion from which I've learned a great deal it seems to me that there are something like two or three generally alternative regimens and that really shrewd people here are using different regimens equally successfully If these really are equivalent then to the best of our knowledge one ought to be able to set up a randomized trial in which these treatments are allotted at random to alternate patients We could then discover which of the combinations is the best This has been done with streptomycin isoniazid and PAS for the treatment of tuberculosis

Dr Freis Dr Paton such a trial is under way in the Veterans Administration as a cooperative study in which the popularly used regimens have been randomized in a double blind evaluation and this is being carried out over a long period of time

Dr Paton In that case I would be very interested and perhaps other people would to know what the regimens are which are being compared

Dr Freis The regimens are in the mild and moderately severe hypertensives Regimen one is reserpine regimen two is reserpine and hydralazine and regimen three is the placebo of the two In the severe hypertensives regimen one is reserpine plus mecamylamine titrated regimen two is reserpine plus pentolinium and regimen three is reserpine plus chlorisondamine The ganglion blocking agents are put up in equipotent tablets in the form of units so that we don't know which particular blocker we are using A new study is going on in three hospitals in which chlorothiazide is being evaluated in different combinations

Dr Schmidt In screening antihypertensive agents in patients what are the most important qualities of the agent to screen for? Those of you who are making clinical trials of these agents could probably speak to the best effect What are the most important qualities of the agents?

Dr Hoobler I could mention one quality that I think is lacking in most regimens and that is the ability to lower the blood pressure in the recumbent as well as in the standing position equally This is a great deficiency of everything except perhaps reserpine and chlorothiazide

Dr Schmidt The absence of undesired side effects is the obvious one

Dr Paton It is a curious thing but there doesn't seem to be any drug which lowers equally in the upright and supine positions except perhaps cardiac depressants Dr Schmidt do you have any ideas on this?

Dr Schmidt No I don't

DR SCHROEDER Dr Schmidt I think hydralazine is a fairly good one that is effective in both positions except that in sympathectomized patients it is more effective in the upright position When we first got it we thought that perhaps it might have a postural effect because our sympathectomized people were getting dizzy But in all people without sympathectomy it has very little postural effect on the blood pressure so hydralazine is one drug that isn t so bad in that way

DR PATON Is that true if you increase the dose so as to produce a comparable reduction in blood pressure?

DR SCHROEDER Yes that s true at the large dosage levels also That is not true of course when there is a ganglionic blocking agent used with it

DR HOOBLER I thought you said the other day that hydralazine wasn t any good as a hypotensive drug when given alone

DR SCHROEDER No I think Dr Page s group and our group have reported comparable results In about two thirds of the patients there is a significant fall in blood pressure which is better than one would get with salt restriction rice diet or anything else except surgery

DR SCHMIDT Isn t it true that the drugs that have the least tendency to exaggerate postural hypotension are those that act centrally such as reserpine and hydralazine and those that have the greatest tendency for postural effect are those that act peripherally such as ganglion blocking or peripheral blocking agents?

DR SCHROEDER I am quite strongly convinced that hydralazine doesn t work centrally or if so most indirectly but it works entirely on smooth muscle in a kind of long acting nitrite manner

DR MOYER Our clinical results using hydralazine as the only therapeutic agent for treating hypertension were not as good as those obtained by Dr Schroeder

In our series only 35 per cent of 54 patients were responsive to hydralazine alone after three months After one to two years of therapy the number responding was reduced to 9 per cent In another series of 33 patients 57 per cent had a satisfactory initial reduction in blood pressure In this series only 25 per cent of those who were originally started on hydralazine continued to take it for a year These figures hint at the difficulties of keeping patients on this form of therapy

On the contrary when this drug is used in combination with other antihypertensive agents it has proved to be a very useful compound in many patients Rauwolfia and/or chlorothiazide may be added to hydralazine (the Rauwolfia and chlorothiazide should be started first in order to block the cardio accelerator effects of hydralazine) yielding a combination which will effect a greater reduction in blood pressure than would be obtained with either drug given alone The hydralazine should be started in small doses that is 12 5 to 25 mg four times daily and increased by a titration method until an optimal reduction in blood pressure is obtained I think that the dosage of hydralazine should be regulated by the blood pressure readings in the upright position since we observed some patients with a significant or

thostatic response In a small group of patients we treated in this way nearly 70 per cent responded to treatment

Hydralazine although of limited value when administered by the parenteral route is useful in the treatment of acute glomerular nephritis and toxemia of pregnancy in which diseases it has some specificity of action Best results are obtained when this drug is used in combination with reserpine The onset of action (15 to 20 minutes) of hydralazine after parenteral administration is much more rapid than that of reserpine Therefore it is given to patients in whom a rapid onset of action is a necessity or in those who do not respond adequately to reserpine alone

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Editors Note

Much has been said about the lupus like syndrome (hydralazine disease") associated with hydralazine administration being related to large doses primarily I should like to submit a case report given to me by Dr Gordon Bendersky The patient is reported to have developed this syndrome while taking 100 mg per day only and died because of an intestinal hemorrhage

This case is not being presented to indict the drug When the drug is indicated it should be used but when used it should be employed in doses which are adequate to produce the desired response Doses up to 400 mg may be employed but if the desired response is not forthcoming the drug should be discontinued since even small doses may in a small number of patients have serious effects The drug should probably always be given in combination with Rauwolfia and chlorothiazide

A Case of Fatal Hydralazine Disease with Massive Intestinal Bleeding Associated with Extensive Necrotizing Arteritis

Gordon Bendersky M D and Carlos Ramirez M D
Hahnemann Medical College and Hospital

M E a 72 year-old white female was admitted to Hahnemann Medical College and Hospital on March 30 1958 because of sudden hemorrhage into her bowel She had received 100 mg of hydralazine (Apresoline) daily for two years for mild hypertension and remained well until petechiae developed on the lower extremities three days prior to admission She arrived in the hospital in shock with a blood pressure of 60/40 demonstrating the presence of grade I arteriosclerotic retinopathy scattered nonconfluent petechiae and small purpuric lesions on the lower extremities and abdomen No congestive failure nor arthropathy was evident Proctosigmoidoscopy revealed actively continuing bleeding which obscured adequate visualization no mucosal purpuric or ulcerative lesions were found Bleeding coagulation and prothrombin times were normal clot retraction was normal a gastrointestinal series of x rays were normal She was transfused with 4 liters of whole blood returning the hemoglobin from the initial 6 4 gm per cent (hematocrit of 26) to 12 gm She suddenly died on April 3 1958 after a period of acute pulmonary edema No steroids had been administered

Autopsy revealed the presence of shallow irregular ulcerations varying in size from 2 to 8 mm in diameter in the mucosa of the last portion of the jejunum and that of the ileum Generalized arteriosclerosis and a calculous gallbladder were also noted Microscopically the heart showed hyaline degeneration of some collagenous fibers and arteriolar intimal thickening with fibrinoid degeneration The kidney demonstrated the presence of fibrinoid "wire-loop glomerular basement thickening as well as fibrinoid degeneration of the medium sized arteries In the small intestinal submucosa were noted thickening

and fibrinoid necrosis of the media and intima of medium sized arteries with mononuclear cell infiltration

This is the first reported case of hydralazine disease in which death was associated with massive intestinal bleeding and mucosal ulcers resulting from necrotizing vasculitis and fibrinoid degeneration Unique also is the renal glomerular wire looping attributable to hydralazine Relatively small dosages of hydralazine may therefore be provocative of disseminated collagen disease simulating systemic lupus erythematosus

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DR SCHMIDT Should antihypertensive drug therapy be limited to the more severe cases of hypertension which already show organic damage?

DR FINNERTY I am sure that the average patient who comes to the doctors office shows very little vascular disease and this is the patient with the blood pressure that is high whose fundi are normal whose heart is normal and there is no clinical evidence of kidney damage What does the doctor do with this kind of patient? This is a real problem I ve been here now three days and I haven t heard much about the fact that stress and anxiety are frequently associated with the blood pressure that is high Whether you feel that reserpine is a good or a bad drug as far as lowering the blood pressure is concerned it certainly is as good as Sodium Amytal for relieving anxiety The practitioner must treat this kind of patient the patient without vascular disease who will do well with a grain of Sodium Amytal three times a day—or reserpine in small doses if you happen to be of that school

DR BEYER I have been interested in this question from the standpoint of pharmacologic approach to preventive medicine Whether you are talking about a neurogenic type of hypertension or some other form I think all of the discussion today has indicated that as you can reduce or maintain a normal blood volume so you can also reduce blood pressure I have a feeling that if one can in some way modulate the electrolyte balance to the favor of the patient thus in the long range will help a lot This is to say that the type of therapy represented by the diuretics such as chlorothiazide and the like should be started early and not after the late pathology has developed I don t think you can reverse the pathology If therapy is started early you can arrest the progression of the disease at an early stage rather than trying to reverse a disease process which has already progressed to the point that you know you can t do anything about it Part of this feeling is based on the fact that as somebody said this morning hypertension begets hypertension in the sense that as one develops an increased vasoconstriction this contributes to the pathogenesis of the later changes associated with hypertension Indeed these changes contribute ultimately to the changes in arteriosclerotic hypertension I am talking now from more or less the theoretical standpoint Perhaps those who are dealing with this problem every day would look at it quite differently

DR HEIDER If we were to subscribe to the idea that hypertension ultimately ends up in producing damage to one organ or another we are forced into having to treat it This disease starts somewhere and it progresses—its not here today and gone tomorrow I believe that the sooner you treat it the better

DR BEYER This is in large measure contingent on a safe form of therapy

DR SCHROEDER I think that is right Dr Beyer but we haven t got a completely safe form of therapy yet So I think we have to progress in stages Obviously when we evaluate the status of a patient we take our chances with the severe or fatal side effects of any regimen that is either surgery or drug therapy And when the chances of the drug doing harm are less than the disease then we take the chance and treat the disease As we find drugs that are less and less toxic we are allowed to treat milder and milder cases I think our aim is to treat every case as you indicate But I don t think we are ready to do that now If we do we are going to have a country of reserpinized people which is not good for the economy

DR HOOBLER I think it is important from a psychiatric viewpoint that when you start a young person on an antihypertensive drug and you can t succeed in bringing his pressure down then you run the risk of really making him feel trapped You can approach therapy with the idea of "We ll try to lower the pressure and if it works fine If it doesn t work you are in no danger anyway" This type of psychotherapy should certainly be introduced in *every early* case My other point is that the early case of hypertension generally responds better to these milder treatments and is more easily handled Perhaps this is an argument for starting therapy early

In our Clinic now we start therapy in young people when their blood pressure on repeated casual readings reaches 160/100 We start using one of the mild therapeutic regimens reserpine and chlorothiazide until we are satisfied that it is either a failure or that we have brought the blood pressure down and then we follow the patient carefully The most important thing is to follow the patient indefinitely for the resurgence of hypertension

DR SCHMIDT Any other comments on this one?

DR DAESCHNER I think there is one practical point which determines what you are going to do in these cases and that is your definition of early organic damage If you take the kidney as the organ for examination certainly the BUN is a rather late evidence of organic damage Function tests such as renal plasma flows and glomerular filtration rates may be misleading We have found patients who had quite good plasma flows and glomerular filtration rates but who by biopsy showed rather significant renal lesions As a result I think that you are almost forced to treat the earliest hypertension that looks real rather than wait for something which you may not be able to find until it is too late

DR SCHMIDT I conclude then that the panel would agree to early treatment and that it should not be limited to severe cases of hypertension who already have organic damage

Do any of the drugs used exert a specific action?

DR GROLLMAN I d say that despite the fact that antihypertensive drugs do not exert a specific action in the sense of correcting the basic disturbance nevertheless they should be used because the evidence is perfectly clear that the elevation of pressure *per se* regardless of its initial cause is in itself detrimental The blood pressure helps to bring on the complications that

finally kill the patient I think the evidence for that is accumulating in our clinical observations regarding the behavior of patients that are treated We have tabulated data and actual figures beginning with Dr Smithwick's publication showing the effect on longevity of patients on whom he performed sympathectomy More recently some data which have been presented at this meeting have shown the beneficent effect of therapy that is therapy which merely lowered blood pressure and did not have any specific effect on the underlying disturbance And a final bit of evidence when experimental animals are observed in which one uses some of the nonspecific methods to lower blood pressure practically all of those will be alive when the control animals are dead which proves that lowering blood pressure by methods that are nonspecific is effective

DR SCHROEDER I have to disagree slightly with Dr Grollman I am not sure that some of these therapeutic effects are not specific I think the question ought to be left open We cannot give a categorical no" to say that altered sodium or potassium or magnesium in the smooth muscle cell isn't perhaps a specific change I don't think one can say that a drug that dilates constricted vessels no matter what constricts them may not be working on something basic to vasoconstriction which is altered in hypertension I don't think that by cutting nerves we are doing something nonspecific when a good many of us believe that nerves have something to do with the onset and development of hypertension I think that question ought to be left open so that we can search for the specific abnormality and perhaps get a clue to the basic disturbance because of effective therapy

DR SCHMIDT We may be getting into semantic difficulties here It's a matter of definition of terms but basically we all agree that nobody knows enough about the fundamental mechanisms to know whether these drugs do or do not act specifically

B SPECIAL PROBLEMS IN THE THERAPY OF HYPERTENSION

Treatment of Hypertension in Childhood with and without Renal Disease

C WILLIAM DAESCHNER AND WARREN F DODGE
Baylor University College of Medicine

Children who develop arterial hypertension may be placed conveniently in two categories namely those in whom the hypertension is associated with a preceding renal disease and those in whom renal changes are absent or occur only as secondary phenomena Although a renal basis for hypertension in children is most common the nonrenal causes are important since they frequently represent curable types of hypertension In addition their prompt recognition by the physician may prevent serious secondary renal changes The determination of blood pressure in the child is therefore as important as it is in the adult

Although normal blood pressure in children varies somewhat with age a more significant variable is the selection of the proper cuff to fit the child s arm A cuff which is too narrow will give falsely high readings and conversely a cuff which is too wide will give the misleading impression that the blood pressure is low Several methods are recommended for the selection of a cuff of the proper size One is that the cuff when applied should cover approximately two thirds of the upper arm segment For this purpose the physician must have several cuffs of varying size or for simplicity he may fold a regular cuff lengthwise to an appropriate width before application Normals by this method are discussed by Gunteroth and Nadas [1] Another approach which we have found useful is using the "tail" of the cuff to measure the circumference of the arm (or leg) then folding the cuff to a width equal to half the circumference of the part to which the cuff will be applied This method in our experience yields fairly consistent average blood pressures of 105 ± 15/ 70 ± 15 throughout childhood As important as the selection of the cuff is the careful application of the cuff to the arm (or leg) so that it fits evenly and does not bulge when inflated

With newborn and premature infants special procedures such as the flush technique described by Goldring and Woltmann[3] may be necessary to secure an approximation of arterial pressure However for the majority of children the standard techniques outlined above are entirely satisfactory and allow little excuse for the all too common omission of blood pressure determination from the physical examination of children

In the discussion to follow the outline of the conditions associated with hypertension in children as shown in Table 1 will be followed Where appropriate illustrative case examples have been included for emphasis

TABLE 1 RELATION OF HYPERTENSIVE CARDIOVASCULAR DISEASE AND RENAL DISEASE IN CHILDREN

- A Hypertension associated with renal disease
  - 1 Congenital anomalies
    - a Cystic disease of the kidney
    - b Hydronephrosis (obstructive or neurogenic)
    - c Uretero pelvic junction obstruction
  - 2 Infections
    - a Chronic pyelonephritis
    - b Unilateral atrophic kidney
  - 3 Hypersensitivity states
    - a Acute glomerulonephritis
    - b Chronic glomerulonephritis
    - c Collagen diseases
    - d Nephrotic syndrome
  - 4 Miscellaneous
    - a Renal tumors (Wilms s tumor)
    - b Radiation injury
    - c *Hurler s disease*
- B Hypertension not due to primary renal disease
  - 1 Iatrogenic
    - a Anxiety and fear
    - b Vasopressor agent therapy
    - c Adrenal steroid or corticotropin therapy
  - 2 Cardiac
    - a Coarctation of the aorta
    - b Valvular stenosis congenital aortic
    - c Patent ductus arteriosis
    - d Rheumatic heart disease with aortic insufficiency
  - 3 Endocrine
    - a Hyperthyroidism
    - b Cushing's disease
    - c Pheochromocytoma
    - d Primary aldosteronism
    - e Congenital adrenal hyperplasia
  - 4 Miscellaneous
    - a Hypercalcemic states
    - b *CNS disease*
    - c Anoxia
    - d Idiopathic or essential hypertension

HYPERTENSION WITH RENAL DISEASE*

Congenital Anomalies *Cystic disease of the kidney* may be represented by either multiple cysts involving both kidneys or single unilateral cysts The former condition is frequently familial and the degree of cystic change varies from that compatible with a normal life span to that whereby a mass of cysts replaces the kidney and death from renal insufficiency occurs in the newborn period No satisfactory treatment of the primary condition is available however *symptomatic control of the blood pressure may* allow the patient to lead a more normal life

R L a 6 year old colored female was first seen because of headaches and gross hematuria She was found to have marked hypertension but examination revealed little else Although the hematuria gradually cleared over a two week period the blood pressure of 180/120 showed no tendency to return to normal Intravenous pyelography revealed the typical pattern of polycystic disease Reserpine (0 25 mg) and mecamylamine (5 mg) given three times a day led to a gradual reduction in her blood pressure to 140/90 She is in school alert active and free of headaches she has shown a normal weight gain and height growth

Hydronephrosis secondary to mechanical or neurogenic obstructive factors may be unilateral or bilateral depending on the site of the obstructive lesion The significance of the lesion to the patient will depend upon the location and degree of obstruction as well as its duration and the consequent damage to the kidney Infection is common and further contributes to the renal parenchymal destruction

* In the following discussion GFR refers to the glomerular filtration rate measured by the clearance of inulin ERPF refers to the effective renal plasma flow measured by the low level clearance of para aminohippurate Tm PAHA refers to the maximum tubular excretory capacity for para aminohippurate and MBP refers to the mean blood pressure in mm Hg calculated as the diastolic pressure plus one third of the pulse pressure For details see reference 4

M H a 9 year-old white male was referred by the school nurse because of poor progress in school He appeared malnourished poorly developed but not acutely ill Blood pressure was 170/110 Abdominal examination revealed a large suprapubic mass and postvoiding catheterization yielded 350 cc of residual urine The patient stated that he always had trouble emptying the bladder and frequently noted involuntary loss of a few drops of urine Urinalysis revealed a specific gravity of 1 016 and pH of 6 5 The BUN was 42 mg per cent Urologic studies demonstrated severe bilateral hydronephrosis and an atonic bladder Renal function studies showed a GFR of 27 cc /M²/minute (normal 70 cc) and an effective renal blood flow of 290 cc /M /minute (normal 600 cc) Catheter drainage and later a plastic surgical procedure relieved the obstructive disease and reserpine therapy gradually reduced his blood pressure to a level of 135/90 The postoperative course was complicated by several infections in spite of which the patient did well Repeat studies of renal function six months later when blood pressure was still 135/90 showed a GFR of 29 cc /M /minute and an ERBF of 260 cc /M /minute His blood pressure three years later is 135/85 and his weight 82 pounds He is receiving only moderate amounts of reserpine and no ganglionic blocking agent

Obstruction of the uretero pelvic junction is listed by most authors as a common anomaly either due to primary malformation of the junctional tissue with resulting obstruction or associated with pressure of an aberrant renal artery Secondary pyelonephritis of the involved kidney is common and is the usual reason for the patient s seeking medical advice It is important that the physician suspect and seek an anatomic obstructive lesion as the underlying basis for the patient s acute infectious process The obstruction is usually unilateral and damage to the kidney is often extensive before significant hypertension appears Treatment of the infection relief of the obstruction and where indicated removal of the severely damaged kidney usually lead to a return of the blood pressure to normal

Infections *Primary chronic pyelonephritis* as a cause of hypertension in childhood is rare However pyelonephritis in association with obstructive lesions of the genitourinary tract as mentioned earlier is not uncommon Hypertension when it occurs is usually a late complication of chronic pyelonephritis The therapeutic problem then involves the relief of the anatomic obstruction as well as the identification of the etiologic agent and the prescription of appropriate antibiotic or chemotherapeutic drugs Emphasis should be placed upon the careful selection of the proper agents as indicated by *in vitro* sensitivity tests In our exerience better results have been obtained and fewer relapses have occurred through the utilization of the combination of a parenterally administered bactericidal agent (penicillin streptomycin kanamycin or vancomycin) plus an orally administered bacteriostatic drug (tetracycline Chloromycetin novobiocin sulfonamides or Furadantin)—the former to be given for two weeks and the latter to be continued for an additional three to four months This problem is discussed in more detail elsewhere in this symposium by E M Yow

The unilateral atrophic kidney associated with hypertension probably has its origin in unrecognized or unsuccessfully treated pyelonephritis in early life The pathogenesis of the lesion includes local obstructive phenomena with infection fibrosis contraction and a resulting renal ischemia leading to hypertension At the time the lesion is recognized the contralateral kidney is usually hypertrophied and the involved kidney virtually nonfunctional At this point the original infection may be inactive or healed Removal of the atrophic nonfunctional kidney usually leads to a reduction in blood pressure to normal and improvement in the patient s general health This lesion should not be confused with the congenital hypoplastic kidney with

its threadlike blood supply which is usually asymptomatic and not a cause of hypertension

N S S was first seen at the age of 9 years with the complaint of severe headaches for two years History revealed that she had experienced episodes of unexplained fever since the age of four years and had been treated each time with short courses of antibiotics She had always seemed to have some trouble in initiating urination Examination revealed a small child (height and weight average for a 6 year old) who did not appear acutely ill or uncomfortable Blood pressure in upper extremities was 170/130 and in lower extremities was 200/140 Funduscopic examination revealed a grade 3 hypertensive retinopathy The heart was moderately enlarged Laboratory examinations were within normal limits Post voiding catheterization revealed a residual urine volume of 125 cc Excretory urograms demonstrated prompt excretion of dye on the left and the delayed appearance of dye on the right The right kidney was noted to be quite small and the left kidney definitely larger than normal Table 2 lists the results of clearance studies The contracted right kidney was removed and on the fourth postoperative day the blood pressure returned to a normal range of 120/80 Improvement in renal function was demonstrated by repeat studies on the sixth postoperative day

TABLE 2 INFLUENCE OF NEPHRECTOMY ON BLOOD PRESSURE AND RENAL FUNCTION IN A PATIENT (N S S) WITH HYPERTENSION AND UNILATERAL ATROPHIC KIDNEY

TIME	BLOOD PRESSURE (mm Hg)	GFR* (cc /min) right	GFR* (cc /min) left	ERPF (cc /min) right	ERPF (cc /min) left	SODIUM (µEq /min) right	SODIUM (µEq /min) left
Preop	170/130	4 8	22 0		91	27	32
Postop 6 da	120/80	—	52 0	—	297	—	134
Normal	105/70	35	35	175	175	—	—

Corrected to 1 0 M Surface Area
Value too low to measure

Hypersensitivity States *Acute glomerulonephritis* represents by far the most common cause of hypertension in childhood Most authors consider an elevation of blood pressure a cardinal part of the diagnostic triad of acute hemorrhagic glomerulonephritis the other two members of the triad being hematuria and edema In the majority of patients hypertension is limited to the acute stage and is not severe In typical patients with acute nephritis there is an initial rise in blood pressure which occurs with or shortly following the first evidence of clinical illness During this period the blood pressure shows marked lability and a tendency to increase for the first three to five days then it tends gradually to fall toward—but usually not to—normal (Fig 1) This initial blood pressure rise parallels the period of reduced urine volume and marked edema and the fall in pressure is usually associated with the period of clinical improvement and increase in the urine volume to near normal value After a variable interval of one to five days the trend in pressure is again upward this may occur at a time when the patient s clinical appearance otherwise continues to improve This second period of elevated blood pressure is usually more persistent and shows less daily variation it may last one to six weeks and then very gradually return to normal In mild acute glomerulonephritis only the first phase hypertension may be present in more severe cases the second phase may be prolonged and difficult to manage In general the blood pressure elevation of the first phase is more responsive to hypotensive therapy than that of the second phase

Characteristically the hypertension associated with acute glomerulonephritis is readily controlled by parenterally administered reserpine and/or hydralazine[4] Doses of reserpine in the range of 50 to 100 µg /kg body

weight given intramuscularly are usually adequate to produce a satisfactory decrease in blood pressure in from one to three hours The pressure then remains down for from 8 to 12 hours and sometimes for 24 hours following a single dose (Fig 1) Because of the individual variations in the duration of effectiveness of a given dose it is desirable to repeat doses not oftener than every 8 to 12 hours and preferably only when a tendency to a rise in blood pressure is detected Patients whose hypotensive response to a single dose as high as 150 µg /kg is not adequate are not likely to respond to higher doses and hydralazine should be added This is usually done on an individual basis by titration initially giving a dose of 5 mg parenterally and noting the hypotensive effect Subsequent doses are then increased as necessary to provide adequate antihypertensive effect It should be emphasized that only parenterally administered reserpine is of value in acute hypertension since the oral form requires 7 to 14 days to influence the blood pressure significantly Parenteral reserpine in large doses sometimes leads to a parkinsonian like state which is reversible when the dose is reduced or omitted

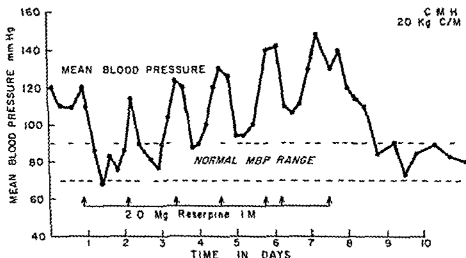


Fig 1 The course of blood pressure in a patient (C M H) with acute glomerulonephritis treated with intermittent doses of parenteral reserpine over an eight day period

C M H a 4 year-old colored male was admitted because of puffiness of the face and bloody urine for five days The parents also noted reduced urine volume and described impetiginous lesions over the lower extremities which had been present all summer Examination revealed edema of his face and ankles with some free fluid in the abdominal cavity The heart rate was 60 and the blood pressure was 160/100 Culture of the skin lesions revealed a beta hemolytic streptococcus The BUN was 38 mg per cent and urinalysis showed many red blood cells with red blood cell casts and a 3+ proteinuria Figure 1 describes the patient s blood pressure course and its response to the intermittent administration of parenteral reserpine By the ninth hospital day the patient s blood pressure remained in the normal range without further antihypertensive therapy The hematuria and proteinuria cleared over a four week period and follow up visits have shown no abnormalities of blood pressure or urinalysis

Chronic glomerulonephritis is less commonly encountered in childhood than in adult subjects However the problem is similar and the hypertension represents a serious sequela Though nothing can be done to reverse the underlying pathology further loss of renal function may be prevented or

delayed through the control of hypertension The degree of renal damage in these patients is usually fairly marked It has been our experience with clearance techniques and renal biopsy to find that the degree of hypertension is frequently out of proportion to the severity of the functional and histologic disturbance Whereas the hypertension of acute glomerulonephritis is usually quite responsive to reserpine (or to reserpine plus hydralazine) the *elevated pressure of chronic nephritis often requires reserpine plus the careful* addition of a ganglionic blocking agent to achieve good control It is our custom to begin with reserpine in fairly large doses (0 25 to 0 5 mg P O every six hours) and after three to four weeks to introduce a ganglionic blocking agent such as chlorisondamine (10 to 25 mg every six hours) or mecamylamine (2 5 to 10 mg every six hours) This is given by mouth and *the dose is gradually increased as needed The usual instructions for the use* of cathartics are given to the patient and his parents The possibility of dizziness and orthostatic hypotension are also mentioned though in our limited experience these have not been a problem in children

W S an 8 year-old white male developed generalized edema hematuria and some hypertension at the age of two years He was hospitalized and followed as an example of the nephrotic phase of glomerulonephritis His course was characterized by continuous proteinuria and intermittent episodes of edema At the age of five years at a time when the patient was free of edema he experienced three convulsions following which there was a right hemiplegia He was seen in the hospital and in addition to the above found to have a blood pressure of 240/160 in both arms and legs His condition was critical Symptomatic treatment of his hypertension with parenteral reserpine produced a definite but incomplete reduction in blood pressure Renal studies revealed better function than

TABLE 3 INFLUENCE OF PROLONGED ANTIHYPERTENSIVE THERAPY UPON RENAL FUNCTION IN A PATIENT (W S) WITH CHRONIC NEPHRITIS

TIME	MEAN B P (mm Hg)	GFR (cc /min)	ERPF* (cc /min)	TM PAHA (mg /min)
Before Rx	211	37	290	—
Rx + 2 hrs	160	39	334	—
Rx + 7 mo	135	40	275	—
Rx + 18 mo	124	35	304	14
Rx + 38 mo	100	39	220	22
Normal	85	70	350	45

Corrected to 1 0 M Surface Area

anticipated (Table 3) o the systemic use of parenteral and later oral reserpine plus a ganglionic blocking agent (chlorisondamine) was begun with return of the blood pressure to near normal values (Fig 2) Table 3 illustrates the influence of prolonged hypotensive therapy on this patient s renal status Though there is no significant improvement the usual deterioration of renal function which is expected in untreated severe hypertension has not taken place in this patient and he is clinically much improved The hemiplegia has cleared he attends school and has shown some weight gain His height growth how ever has been less than ideal and it is felt that his prognosis is still very guarded

Collagen diseases such as disseminated lupus erythematosus and periarteritis are frequently associated with renal pathology and hypertension *These conditions occur most frequently in older children and affect females* more often than males The presence of proteinuria hematuria and other evidences of renal disease in the course of a collagen disease suggests that the prognosis is grave and that adrenal steroid therapy may not be com

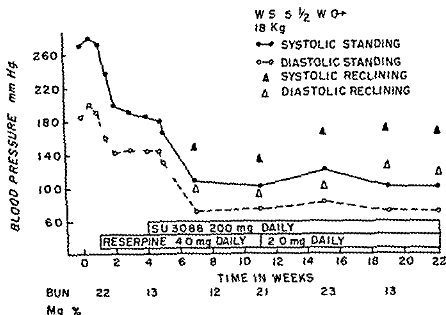


Fig. 2 The response of blood pressure in a patient (W S) with hypertension and chronic nephritis to treatment with oral reserpine and a ganglionic blocking agent (chlorisondamine)

pletely successful in controlling the disease The clinical manifestations of the disease such as headache however may be relieved by treatment directed at the reduction of blood pressure Steroid therapy of the collagen disease in doses sufficient to control signs and symptoms often increases the tendency to elevation of blood pressure It is therefore our practice to treat these patients with appropriate doses of steroids—usually one of the delta 1 derivatives prednisone prednisolone or triamcinolone—and simultaneously to treat the blood pressure with reserpine

D E a 12 year old colored female was first seen because of swelling of extremities and multiple small blisters over the trunk of five months duration At the time of admission there was generalized edema and there were large vesicles over trunk neck face and extremities in a serpiginous distribution The heart was grossly enlarged and the blood pressure was 130 90 Urinalysis showed 4+ proteinuria and occasional red blood cells Bone marrow examination was negative for L E cell The clinical findings plus a skin muscle and later renal biopsy confirmed a diagnosis of collagen disease non-specific type She was treated with prednisolone (10 mg every six hours) and reserpine (0 5 mg every six hours) Over a six month period the skin lesions gradually improved the edema cleared and the heart size decreased The proteinuria has persisted unchanged and the blood pressure has gradually increased to a level of 150/100 As the systemic signs improved the steroid dose was gradually reduced she is now on triamcinolone (2 0 mg every eight hours) Renal function studies reveal a GFR of 44 cc /M /minute an ERPF of 3.0 cc M minute and a Tm PAHA of 33 mg M /minute Although steroid therapy seems to have improved her general condition the renal disease and hypertension appear to be progressing

The nephrotic syndrome is the general term applied to patients who in the absence of known antecedent renal disease demonstrate the onset of marked generalized edema massive proteinuria hypoproteinemia and hyperlipemia The most common form of this syndrome seen in childhood is the

delayed through the control of hypertension The degree of renal damage in these patients is usually fairly marked It has been our experience with clearance techniques and renal biopsy to find that the degree of hypertension is frequently out of proportion to the severity of the functional and histologic disturbance Whereas the hypertension of acute glomerulonephritis is usually quite responsive to reserpine (or to reserpine plus hydralazine) the elevated pressure of chronic nephritis often requires reserpine plus the careful addition of a ganglionic blocking agent to achieve good control It is our custom to begin with reserpine in fairly large doses (0 25 to 0 5 mg PO every six hours) and after three to four weeks to introduce a ganglionic blocking agent such as chlorisondamine (10 to 25 mg every six hours) or mecamylamine (2 5 to 10 mg every six hours) This is given by mouth and the dose is gradually increased as needed The usual instructions for the use of cathartics are given to the patient and his parents The possibility of dizziness and orthostatic hypotension are also mentioned though in our limited experience these have not been a problem in children

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Rx + 38 mo	100	39	220	22
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Corrected to 1 0 M Surface Area

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Collagen diseases such as disseminated lupus erythematosus and periarteritis are frequently associated with renal pathology and hypertension These conditions occur most frequently in older children and affect females more often than males The presence of proteinuria hematuria and other evidences of renal disease in the course of a collagen disease suggests that the prognosis is grave and that adrenal steroid therapy may not be com

TABLE 4 INFLUENCE OF WILMS'S TUMOR OF THE KIDNEY (RIGHT) ON RENAL FUNCTION AND BLOOD PRESSURE (J S)

TIME	BLOOD PRESSURE (mm Hg)	GFR (cc/min) right	GFR (cc/min) left	ERPF (cc/min) right	ERPF (cc/min) left	NA EXCR. (µEq/min) right	NA EXCR. (µEq/min) left	HCT
Preop	145/110	5 4	11 5	24	44	68	54	37
Postop (23 days)	95/60	—	70	—	255	—	130	44
Normal	105/70	35	35	175	175	—	—	—

Values corrected to 1 0 M Surface Area

Radiation nephritis or renal lesions due to the effects of roentgen ray irradiation have been produced experimentally and are occasionally reported clinically as a consequence of radiotherapy administered to tumors in the renal area The symptoms appear in from a few days to several months after radiation therapy and the findings are similar to those of chronic glomerulonephritis azotemia proteinuria microscopic hematuria anemia and intermittent edema Hypertension and cardiac enlargement were present in all reported cases Microscopic examination of the kidney reveals diffuse damage to glomeruli tubules and arterioles with atrophy and fibrosis Since there is at present no treatment for this condition prevention is essential When radiation therapy must be carried out in the renal areas it has been shown that the risk of renal failure may be minimized by protecting the upper one third of each kidney [7] The comparatively undamaged nephrons of the upper pole will then sustain renal function

Hurler's disease or gargoylism has recently been shown to be the result of a defect in metabolism of acid mucopolysaccharides with the excretion of chondroitin sulfate B and heparitin sulfate in the urine [8] In at least one patient heparitin sulfate has been demonstrated in excessive quantities in the liver and it is possible that the stored material in the epiphyseal areas liver kidney spleen and brain is similar The stored material (whatever its chemical composition) in the growing areas of the bones leads to the characteristic chondrodysplastic appearance and the deposits in the brain gradually produce mental deficiency The liver and spleen become markedly enlarged, as do the kidneys The hypertension sometimes seen in these patients is moderate in degree and may well be asymptomatic Hypotensive therapy has little to offer and reserpine in particular only tends to increase the already bothersome nasal congestion

D A was first seen at the age of 34 months with the history that at about 18 months of age her parents began to note a progressive dorso-lumbar kyphosis In the hospital the patient demonstrated the typical facies of gargoylism short thick hands and fingers a dorso-lumbar kyphosis and marked hepatosplenomegaly Blood pressure was 180/100 Radiographic examination revealed "chondrodysplastic" changes in the epiphyseal areas and in the vertebral bodies (particularly marked in the lumbo-dorsal area) Excretory urograms revealed prompt excretion of the dye but both kidneys were noted to be larger than normal Renal function studies revealed a GFR of 66 cc/M /minute and an ERPF of 270 cc/M /minute Reserpine therapy reduced her blood pressure but produced an intolerable degree of nasal congestion and so was discontinued

HYPERTENSION NOT DUE TO RENAL DISEASE

Iatrogenic *Anxiety and fear* are emotional responses common to most people when visiting a physician's office The child who has experienced

many immunization and antibiotic injections is a particularly reluctant visitor to the medical examining room It is not surprising therefore that the child s blood pressure may be elevated and the pulse quickened at the sight of the physician However with time and proper reassurance this problem usually passes Not quite so transient is the elevation of pressure seen in older children in association with family social school or religious tensions These subjects often complain of severe headaches malaise and nervousness The only abnormal physical finding may be a modest elevation of blood pressure Careful inquiry into the environment family history and attitudes and the child s activities may reveal the origin of the patient s anxiety An emotional basis for his symptoms will be completely acceptable to the child and his parents only when renal and other causes of hypertension have been carefully sought and ruled out In some patients the use of an ataractic such as reserpine in doses of 0 1 to 0 25 mg three times a day may be helpful These patients should be watched in the future for signs of more significant and persistent hypertension

G M an 11 year old white male was well until one week prior to admission when he developed a severe headache while running at school He was noted to be pale and dizzy At a physician s office the only abnormal finding was a blood pressure of 170/110 The patient was hospitalized for observation during this period arterial blood pressure determinations varied widely but were usually elevated After several days the values fell to a normal range Intravenous pyelographic studies were normal as was a concentrated urine specimen Regitine produced no fall in blood pressure and the catechol amines were 2 mg /24 hours The patient enjoyed being in the hospital and was reluctant to leave at the time of discharge The father then pointed out that the patient had recently transferred to a new school where the homework was unusually heavy In addition the boy joined the local football team this year for the first time an activity entered into more because of his father s insistence than his own desire Football was discontinued for the remainder of the year the boy was given some help with his school work by an understanding teacher He has remained asymptomatic and his blood pressure is normal

Vasopressor agents as a cause of hypertension in childhood are uncommon even in asthmatic children but their influence should be kept in mind when a child with elevated blood pressure is seen

Corticotropin and adrenal cortical steroid therapy is an increasingly common cause of hypertension in the hospital practice of medicine[9] Although the newer delta 1 derivatives of cortisone and hydrocortisone (prednisone prednisolone triamcinolone and methyl prednisolone) show less tendency to cause disturbances of water and salt metabolism and increases in blood pressure they are by no means devoid of these properties In the massive doses necessary to treat nephrosis collagen diseases and rheumatic fever adrenal steroids frequently produce some elevation of blood pressure This effect can usually be minimized by providing the patient a low salt diet and where necessary by adding parenteral or oral reserpine Marked hypertension is usually not amenable to hypotensive or dietary treatment and is an indication for reduction or withdrawal of steroid therapy Patients with reduced renal function are particularly prone to show marked hypertension in response to steroid therapy and some may even become oliguric and azotemic under these circumstances Steroid therapy in chronic nephritis should therefore be used with great caution and a careful regard for these potential complications

D L a 5 year-old white male developed the nephrotic syndrome at the age of 2½ years He was treated intermittently with ACTH and later steroids with partial loss of

edema but little change in his fairly marked proteinuria For the past year his BUN had ranged from 18 to 28 mg per cent It is also of interest that each period of corticotropin or steroid therapy was associated with a rise in arterial blood pressure Because of the severe edema and proteinuria with marked hypoproteinemia and hyperlipemia he was given another trial of steroid therapy Base line blood pressure was 110/80 and after several days of observation he was begun on triamcinolone 10 mg every six hours On the sixth day of treatment blood pressure rose to 160/110 and in spite of reserpine therapy it remained at this level By the twelfth day of treatment there was increasing abdominal fluid and on the twentieth day marked ascites and reduced urine volume These findings plus a rising BUN led to paracentesis and the withdrawal of steroid therapy The patient then gradually lost most of his edema as the urine volume increased and the BUN returned to normal

Cardiac *Coarctation of the aorta* is the most common cardiovascular condition causing systemic hypertension in childhood Usually the degree of hypertension is not marked Depending upon the location of the stenosed aortic segment one or both upper extremities may show an elevated blood pressure Though pulsations in the lower extremities are difficult to palpate because of the narrow pulse pressure the actual mean blood pressure in the lower extremities is not low Resection of the aortic defect relieves the vascular abnormality and the blood pressure gradually returns to normal

R L C an 11 year-old white male two months prior to admission developed gross hematuria and moderate proteinuria Examination revealed hypertension in the upper extremities (blood pressure 160/100) but a very weak femoral pulse and no obtainable blood pressure in the lower extremities Urinalysis at the time of hospitalization revealed marked microscopic hematuria 1+ proteinuria but no casts Blood chemical examinations were all normal Angiography demonstrated an area of coarctation of the thoracic aorta below the level of the subclavian artery Because of the hematuria renal function studies were carried out preoperatively (Table 5) repeated in one week and then eight months following resection of the stenosed aortic segment The immediate post operative studies suggested a relative renal hyperemia which had disappeared eight months later The hematuria cleared about two months following surgery and all subsequent urinalyses have been normal

TABLE 5 INFLUENCE OF SURGICAL RESECTION OF A COARCTATION OF THE AORTA ON BLOOD PRESSURE AND RENAL FUNCTION (R L C)

TIME	BLOOD PRESSURE (mm Hg)	GFR (cc /min)	ERPF (cc /mm)
Preop	160/100	87	299
7 days Postop	1[illegible]0/100	99	339
8 months Postop	1[illegible]5/75	76	293
Normal	105/70	70	350

Values corrected to 1 0 M Surface Area

Congenital aortic valvular stenosis in childhood is usually associated with a diastolic elevation of blood pressure and a narrowing of the pulse pressure The presence of the characteristic harsh systolic murmur and thrill over the aortic area transmitted to the neck vessels suggests the malformation

Patent ductus arteriosus when large may be associated occasionally with a mild elevation of systolic pressure in late childhood However the diastolic pressure is low and the pulse pressure is wide so the mean blood pressure is normal

Rheumatic heart disease with severe aortic valvular insufficiency is sometimes associated with a moderate systolic hypertension and widening of pulse pressure

Cardiac failure of severe degree on any etiologic basis may be associated with a rise in diastolic blood pressure and consequent narrowing of pulse pressure associated with increased peripheral vascular resistance due to tissue anoxia

Endocrine *Hyperthyroidism* in childhood, though not common occurs with sufficient frequency to be considered here As in the adult the changes in blood pressure are associated with a rapid pulse a high cardiac output and low diastolic pressure leading to a wide pulse pressure Cardiac failure is uncommon in childhood hyperthyroidism in the absence of underlying organic heart disease although some degree of left ventricular hypertrophy is usually present Reserpine therapy has been shown by Canary et al to effectively relieve or mask the clinical signs and symptoms of hyperthyroidism though it does not appear to affect the hyperfunctioning state of the thyroid gland [10]

A S was first seen at the age of 3½ years with the history that one to two months earlier he had begun to lose weight to be extremely nervous and to sweat excessively Examination revealed a malnourished anxious trembling child who was sweating profusely There was bilateral exophthalmos and marked enlargement of the thyroid gland The pulse ranged from 140 to 160 and the blood pressure range was 140 to 160/60 to 70 The uptake of a tracer dose of I^{131} was 68 per cent in 24 hours and the protein bound iodine was 12 μg per cent In the untreated state his GFR was 130 cc /M /minute (normal 70) the ERPF was 565 cc /M /minute (normal 350) the hematocrit was 35 and the Tm PAHA was 53 mg /M /minute (normal 45) The patient was treated with oral Tapazol (10 mg /six hours) The clinical and laboratory evidence of the hyperthyroid state cleared over a six to eight week period A gradual reduction in the size of his thyroid gland to normal occurred in the next 8 to 12 months

Cushing s disease is a rare endocrine disorder of childhood and is more often associated with an adrenal carcinoma than with diffuse hyperplasia of the adrenal The patient usually demonstrates typical girdle obesity hirsutism acne seborrhea a florid complexion striae and arterial hypertension Laboratory studies reveal polycythemia a hypokalemic hypochloremic alkalosis and a variable increase in the urinary excretion of 17 OH corticosteroids Treatment consists of careful preoperative preparation and subsequent surgical removal of the involved adrenal gland or in the case of diffuse hyperplasia the subtotal removal of both glands Replacement therapy with cortisone (or related corticosteroids) is carried out as indicated Hypotensive drug therapy has little to offer these patients and is probably not indicated

Pheochromocytoma of adrenal medullary or sympathetic origin has been described infrequently in the pediatric age group Nevertheless since it often represents a completely curable type of hypertension it should be considered Hypertension in children due to pheochromocytoma is usually sustained rather than paroxysmal though short periods of more marked elevation of blood pressure may occur as superimposed episodes [11] Nervousness anxiety excessive sweating and headache are all common symptoms constipation polyuria polydipsia weight loss and palpation are not infrequently present Regitine in doses of 1 to 5 mg or piperoxane in doses of 5 to 10 mg leads to a prompt fall in blood pressure For diagnostic studies the intravenous or intramuscular routes are preferred The recent development of accurate laboratory methods for the quantitative estimation of urinary catechol amines offers an even more specific test for the presence of excessive epinephrine and norepinephrine secretion In patients with cardiac

hypertrophy or frank cardiac failure the medical control of hypertension with oral regitine may be necessary and very helpful in preparing the patient for surgery Surgical removal of the tumor is an exacting process since the mass is often small and difficult to locate Adjunctive use of intravenous regitine or Neo-Synephrine may be necessary during the surgical procedure and in the period immediately following tumor ligation

W B a 4 year-old white male was well until the age of 2 years when he developed the progressive onset of irritability headache night sweats weight loss polyuria polydipsia and constipation Minimum proteinuria plus polydipsia polyuria and dilute urine specimens suggested chronic nephritis however a concentration test readily led to a urine specific gravity of 1 028 Intravenous pyelography suggested a mass in the right suprarenal area and intravenous regitine and benodioxane tests each produced a prompt reduction in blood pressure While the patient was maintained on oral Regitine for two weeks he was asymptomatic and gained weight The tumor was then removed The child is now 9 years old and has had no further difficulties his weight gain and growth in subsequent years have been normal

Primary aldosteronism due to an aldosterone secreting adenoma of the adrenal cortex or bilateral cortical hyperplasia is a recently recognized condition first described by Conn Instances of this condition in the pediatric age group have also been described[1] These patients show marked hypertension with a consistently demonstrable hypokalemic hypochloremic alkalosis often associated with episodes of marked muscular weakness[15] Treatment consists in the localization and removal of the hyperfunctioning adrenal cortical tissue

Congenital adrenal hyperplasia with either virilism in males or pseudohermaphroditism in females represents a partial defect in the adrenal cortical synthesis of hydrocortisone In the classic form there is a defect at the level of 21 hydroxylation and hypertension is not present In certain forms of this syndrome however there is a defect in 11 hydroxylation so that excessive amounts of 11 desoxycorticosterone (DOC) and 11 desoxy 17 hydroxycorticosterone (Cpd S) are formed[14] These patients have hypertension presumably in association with the excess DOC and Cpd S production Diagnosis of congenital adrenal hyperplasia is based upon the finding of elevated urinary levels of 17 keto steroids and pregnanetriol in hypertensive subjects the diagnosis is based upon the finding of the reduction product of Cpd S in the urine as well Replacement therapy with hydrocortisone removes the excessive stimulation of the adrenal gland by corticotropin thereafter the production of DOC and Cpd S decreases as the hypertension and other abnormal clinical features of congenital adrenal hyperplasia gradually recede

Miscellaneous *Hypercalcemic states* may exist in relation to hyperparathyroidism multiple myeloma the milk alkali syndrome vitamin D intoxication prolonged immobilization and idiopathic hypercalcemia In children the first three conditions are extremely rare and the others are uncommon The mechanism of the hypertension associated with hypercalcemia is obscure but Goormaghtigh has shown in dogs that hypertension appears to be related to the appearance of lesions in the media of the renal arterioles as well as to the marked deposition of calcium along the basement membrane of the renal tubules[15] Haddy has shown experimentally that acute calcium infusions cause arteriolar constriction when blood values exceed 13 mg per cent[15]

Expanding lesions of the central nervous system in children as in adults may lead to arterial hypertension In general the more rapidly expanding lesions are associated with the more severe and acute hypertension Central nervous system disease as a cause of hypertension has been described in relation to encephalitis hemorrhages infections trauma cerebral anoxia and lead poisoning as well as intracranial tumors The elevation of blood pressure is usually transient and spontaneous or therapeutic alleviation of the primary disorder is associated with a return of the blood pressure to normal

Anoxia and hypertension are not an uncommon clinical combination in patients with severe bronchiolitis asthma or respiratory muscle paralysis and in patients who are receiving artificial respiration The exact role of anoxemia and hypercapnea in the production of hypertension in these conditions is debated and since the hypertension is mild treatment of the primary disease or condition is usually the only indicated therapy

Essential or idiopathic hypertension in childhood is rare Those patients described have the classic signs and symptoms of hypertension namely headaches convulsions poor weight gain cardiac enlargement and retinal vascular changes The diagnosis of essential hypertension is established only after exhaustive search for specific etiologic factors (Table 1) has been unrevealing It is a diagnosis to be entertained only when all known causes of hypertension have been excluded The therapeutic use of oral reserpine in progressively increasing amounts to tolerance (i e the onset of prominent side effects) is recommended by Haggerty[1] with gradual addition of ganglionic blocking agents as necessary in patients who are not controlled by reserpine alone

J A was first seen by us because of a blood pressure of 150/100 obtained during a physical examination for headache No other abnormal physical findings were noted Rest in the clinic and repeated blood pressure determinations led to a gradual reduction to 130/85 Urinalysis was negative as were blood chemical studies and intravenous pyelography The patient was followed at intervals for six months on an out patient basis Recorded blood pressures varied from 170/110 to 130/85 Renal function studies done at a time when the blood pressure was 145/90 revealed a GFR of 108 cc /M /minute and an ERPF of 400 cc /M /minute In the hospital histamine and phentolamine tests were negative With bed rest the pressure fell to 130/85 but rose to 150/100 as soon as full activity was allowed Two years later the blood pressure remains 150 to 160/90 to 105 and a recent renal biopsy reveals no evidence of renal disease He is maintained on oral reserpine (0 25 mg three times a day) and is asymptomatic

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Treatment of Hypertensive Emergencies Associated with Essential Hypertension

RAY W GIFFORD JR

*Mayo Clinic and Mayo Foundation**

Crises arise occasionally in the course of essential hypertension and during such crises the prompt reduction of blood pressure becomes urgent to prevent catastrophe

Most spectacular of these emergencies are sudden unexplained exacerbations of hypertension during which the blood pressure reaches astronomical heights threatening the integrity of the cardiovascular cerebrovascular and renal systems Hypertensive crises of this sort are usually but not always accompanied by acute hypertensive encephalopathy characterized by vomiting headache drowsiness and mental confusion with or without transitory focal neurologic signs

Even in the absence of a true hypertensive crisis however emergency reduction of blood pressure is indicated when intracerebral or subarachnoid

The Mayo Foundation Rochester Minnesota is a part of the Graduate School of the University of Minnesota

hemorrhage or acute left ventricular failure suddenly complicates the course of essential hypertension

METHOD OF ADMINISTRATION OF DRUGS DURING HYPERTENSIVE EMERGENCIES

In the treatment of hypertensive emergencies the necessity for prompt therapeutic effect in addition to the inability of most acutely ill patients to take or retain oral medication makes the parenteral administration of hypo tensive drugs highly desirable if not mandatory

Many of the preparations which are commonly used orally in the treat ment of essential hypertension are also available for parenteral administra tion during emergencies These include reserpine hydralazine various preparations of Veratrum as well as ganglion blocking agents (Table 1)

TABLE 1 PREPARATIONS FOR TREATMENT OF HYPERTENSIVE EMERGENCIES

	METHOD OF ADMINISTRATION AND DOSAGE		
PREPARATION	INTERMITTENT INTRAMUSCULAR (mg)	INTERMITTENT INTRAVENOUS† (mg/20 cc)	CONTINUOUS INTRAVENOUS‡ (mg/L)
Reserpine	2 5–10	2 5–5 0	–
Hydralazine hydrochloride (Apresoline)	20–60	20–40	50–100
Veratrum			
Alkavervir (Veriloid)	0 8–1 5	2 0	4 0
Protoveratrines A and B (Veralba)	0 1–0 4	0 2	2 0
Cryptenamine acetate) (Unitensen acetate)	1 0–2 0	2 0	4 0
Ganglion blocking drugs			
Hexamethonium chloride	15–100	15	250–1000
Pentolinium tartrate (Ansolysen tartrate)	5–50	5	50–150
Chlorisondamine chloride (Ecolid)	2 5–25	–	–
Trimethaphan camphorsulfonate (Arfonad)	–	–	1000
Sodium nitroprusside§	–	–	60

Start with smallest dose increase dose and adjust frequency of injections according to response of blood pressure

† Record blood pressure continuously while injection is made rate of injection should not exceed 0 5 cc per minute and should be stopped frequently when blood pressure is falling to avoid hypotension

‡ Rate of administration adjusted to maintain blood pressure at desired level Solutions can be made more dilute or more concentrated to accommodate fluid requirements of patient Blood pressure should be recorded every 15 to 30 minutes after it has stabilized at desired level

§ Not available commercially for parenteral administration See text

Most of the commercially available preparations can be given intramus cularly by starting treatment with the smaller dosages indicated in Table 1 The dose can be increased and the frequency of injections adjusted according to the response of the blood pressure In this regard it should be emphasized

that the maximal hypotensive effect of reserpine whether administered intramuscularly or intravenously is not obtained for at least two or three hours after injection Consequently repetition of the injection during this latent interval may lead to cumulative effect with excessive hypotension The blood pressure responds much more promptly to intramuscular injections of the other drugs and their hypotensive effect is dissipated more rapidly than is that of reserpine Injections of reserpine therefore are

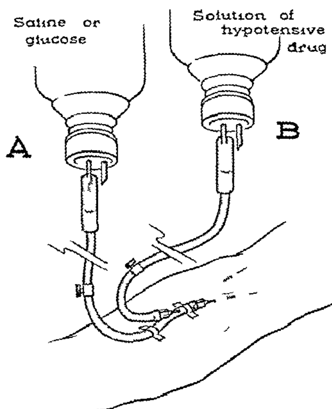


Fig 1 Method for continuous intravenous infusion of hypotensive drugs in treatment f hypertensive crises Use of a Y tube would not permit such prompt initiation or cessation of treatment with hypotensive agents since the tubing from the Y junction to the needle contains a mixture of the two solutions for a time after flow is stopped from from one bottle and started from the other A third bottle (with tubing) containing a solution of levarterenol (4 mg per liter) should be available to replace bottle B and tubing in the event of dangerous hypotension from overdosage

required at less frequent intervals but the physician must anticipate the delayed response to reserpine and must repeat the injection of reserpine sooner after the blood pressure begins to rebound than he would the injection of any of the drugs that act more promptly

Continuous intravenous infusion of hypotensive drugs requires constant supervision by trained personnel because small variations in the rate of administration are often essential to properly controlling the blood pressure This is an advantage as well as a disadvantage If properly executed con

tinuous intravenous administration permits more even control of blood pressure than intermittent injections whether given intravenously or intramuscularly Furthermore excessive hypotension from intravenous overdosage is likely to be of shorter duration for the infusion can be discontinued promptly whereas it is difficult if not impossible to stop or even to retard absorption from an intramuscular depot

To maintain precise control of intravenous infusions two bottles of solution complete with tubing and needles are necessary (Fig 1) The solution in the first bottle (A) contains no hypotensive agent and is used to start the infusion and to keep it running during intervals when the hypotensive drug contained in bottle B is not needed The needle attached to the tubing from bottle A is inserted into the patient's vein while the needle attached to the tubing from bottle B is introduced into the tubing from bottle A as close to the patient as possible This minimizes the length of tubing that will contain a mixture of the two solutions and consequently permits prompt initiation or cessation of treatment After the infusion from bottle A is running into the vein evenly the tubing from this bottle is clamped and the clamp on the tubing from bottle B containing the medicated solution is opened Blood pressure then must be determined every three minutes until it becomes stabilized at the desired level and until the rate of administration which maintains this level is established Even then it is advisable to determine blood pressure at intervals of 15 to 30 minutes

For immediate effect a solution containing one of the Veratrum derivatives or a ganglion blocking agent in appropriate concentrations (Table 1) may be administered intravenously from a 20 cc syringe at a rate that should never exceed 0 5 cc per minute The blood pressure should be determined continuously by another person while the injection is being made When the desired effect is obtained the injection is stopped It may be repeated at intervals as determined by the blood pressure or a continuous infusion of a more dilute solution of Veratrum or ganglion blocking agent is started to maintain the blood pressure at lower levels

Whenever emergency treatment by parenteral administration of potent hypotensive drugs is being carried out for hypertension it is advisable to have a solution of levarterenol readily available for it is an effective antidote for hypotension produced by reserpine Veratrum or ganglion blocking drugs

DRUGS

Reserpine This drug given in doses of 2 5 to 5 0 mg intramuscularly is the drug of choice in most hypertensive emergencies associated with essential hypertension Intravenous administration does not afford more rapid onset of action and consequently has no advantages over intramuscular injections If rapid reduction of blood pressure is desirable it is sometimes helpful to give a ganglion blocking drug or a preparation of Veratrum intramuscularly with the first dose of reserpine Injections of reserpine are repeated as often as indicated to keep the blood pressure at satisfactory levels Individual doses should rarely exceed 10 mg and the total dose in 24 hours should rarely exceed 20 mg Most patients who receive doses of this magnitude for more than a few days exhibit evidence of parkinsonian rigidity which fortunately is usually reversible The soporific effect of large doses of reserpine may be a disadvantage especially in cases of cerebral hemorrhage

or hypertensive encephalopathy when frequent evaluation of the level of consciousness is desirable

Hydralazine Although hydralazine given parenterally is frequently effective in the treatment of hypertensive emergencies associated with eclampsia or acute nephritis I have been impressed by its relative ineffectiveness when used alone in emergencies associated with essential hypertension

Ganglion Blocking Drugs Drugs of this type are potent hypotensive agents but their usefulness in the emergency treatment of acutely ill and bedfast patients is necessarily limited by the fact that their greatest effect on blood pressure is exerted when the patient is in the upright position Whether ganglion blocking drugs are given by intermittent intramuscular injections or as continuous intravenous infusions the doses of these agents necessary to reduce blood pressure significantly for recumbent or even semi recumbent patients are usually so great that paralytic ileus is a frequent complication after two or three days of treatment Retention catheters are nearly always required for elderly men who receive ganglion blocking agents parenterally for any significant period Because of their specific effect in reducing central venous pressure ganglion blocking agents are particularly useful in those hypertensive emergencies associated with acute right or left heart failure Orthopnea usually forces patients in this predicament into a semi recumbent position which makes them ideal candidates for treatment with ganglion blocking agents therefore I routinely employ one of these agents alone or in conjunction with reserpine for this type of emergency To obtain maximal benefit from ganglion blocking agents the patient should be semi reclining and the head of the bed should be elevated on blocks that are 10 inches high

To prevent the somnolence and parkinsonian rigidity produced by reserpine and to avoid the ileus produced by ganglion blocking agents it is sometimes desirable to alternate the use of these two drugs every day or two

Veratrum The range between toxic and therapeutic doses of Veratrum is as narrow when it is given parenterally as it is with oral administration and this seriously limits the usefulness of these otherwise potent drugs Nausea vomiting and bradycardia are frequently encountered when preparations of Veratrum are given parenterally and serious hypotension is more likely to result from use of Veratrum than from reserpine or ganglion blocking agents for bedfast patients For these reasons I reserve Veratrum for those patients whose blood pressure fails to respond to the other drugs

Sodium Nitroprusside When more conventional hypotensive agents are ineffective contraindicated or productive of prohibitive side effects I have used intravenous infusions of sodium nitroprusside with gratifying success (Figs 2 and 3) In my experience it is the most potent drug available for treatment of hypertensive crises

The concentration of the solution can be varied to satisfy the requirements of the patient but ordinarily 60 mg of sodium nitroprusside in a liter of solution has proved satisfactory Within seconds of starting an infusion with such a solution at a rate of 10 to 30 drops a minute the blood pressure drops precipitously and can be brought to and maintained at any desired level by skillful manipulation of the rate of administration The infusion requires constant supervision by trained personnel for small variations in rate of administration often cause wide fluctuations in the blood

pressure (Fig 2) This is the chief disadvantage of this drug In another sense it is an advantage for the effect of sodium nitroprusside is so evanescent that overdosage does not lead to prolonged hypotension within a few seconds after the infusion is stopped or even when its rate is slowed the blood pressure rises promptly (Figs 2 and 3)

Retching perspiration apprehension restlessness and on one occasion muscular twitching were noted when the blood pressure was reduced too rapidly but these symptoms disappeared promptly when the infusion was stopped temporarily and did not reappear with slower rates of administration

Solutions of sodium nitroprusside for intravenous use are not available commercially At the Mayo Clinic the solution is prepared by aseptically adding sodium nitroprusside to a 0 9 per cent sterile solution of sodium

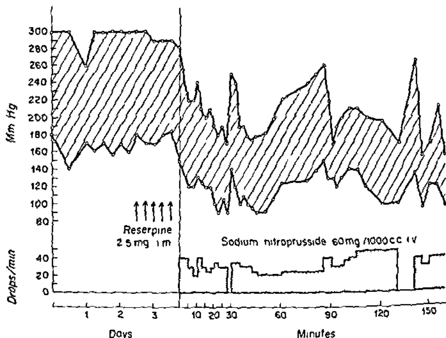


Fig 2 Intravenous administration of sodium nitroprusside promptly reduced the blood pressure for this 37 year-old woman with group III hypertension and hypertensive encephalopathy The time scale is changed to show in more detail the rapid response of the blood pressure to changes in the rate of administration of sodium nitroprusside

chloride but no attempt is made to filter or sterilize the resulting solution We have found it convenient and safe to store in the refrigerator for an indefinite period several brown stoppered bottles each containing 60 mg of sodium nitroprusside in 25 cc of a 0 9 per cent sterile solution of sodium chloride This amount is added to a liter of 5 per cent solution of glucose in distilled water or normal saline solution immediately before it is used

In the past 18 months I have successfully employed infusions of sodium nitroprusside to reduce the blood pressures of five hypertensive patients during periods of crisis that varied from 12 to 96 hours Reserpine given parenterally had proved inadequate for three (Fig 2) hydralazine given parenterally had failed for one and resistance had developed to a combination of reserpine given intramuscularly and hexamethonium given by intra

venous injection to one patient (Fig 3) before treatment with sodium nitroprusside was instituted

The mechanism of the depressor action of sodium nitroprusside is not known Page and colleagues[4] postulated that a direct effect of the nitroprusside molecule is responsible for the immediate fall in blood pressure Chronic oral administration results in significant levels of thiocyanate in the blood but this was not true for any of my patients who received the drug intravenously even for prolonged periods

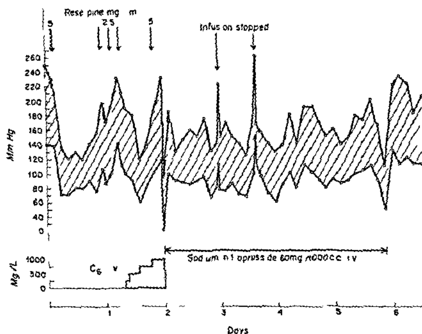


Fig 3 This record shows prompt reduction of blood pressure induced by intravenous administration of sodium nitroprusside to a 49 year-old man with acute cerebral hemorrhage Previous to the administration of sodium nitroprusside this man's hypertension had become resistant to reserpine given intramuscularly and hexamethonium (C_6) given intravenously in gradually increasing concentrations The latter produced early signs of paralytic ileus On two occasions when the infusion containing the sodium nitroprusside accidentally stopped owing to malposition of the needle the blood pressure promptly rose to pretreatment levels

SUMMARY

Hypertensive crisis with or without acute hypertensive encephalopathy cerebral hemorrhage subarachnoid hemorrhage and acute left ventricular failure are emergencies which occasionally punctuate the course of essential hypertension and require prompt reduction of blood pressure

Reserpine given intramuscularly is usually the drug of first choice in dealing with an emergent situation but in the large doses frequently needed it causes somnolence and often a parkinsonian rigidity For more rapid hypotensive effect, a ganglion blocking agent may be given parenterally at the same time as the reserpine Ganglion blocking agents are particularly indicated if congestive heart failure is present because of their direct action in reducing central venous pressure Continuous parenteral use of a ganglion blocking agent frequently leads to ileus and urinary retention The unde

sirable effects of both reserpine and ganglion blocking drugs can be minimized by alternating the use of the two every second day

Sodium nitroprusside given by continuous intravenous infusion is a potent hypotensive agent whose onset and dissolution of action are extremely rapid therefore it requires constant and close supervision It is a useful drug to have available for emergent situations when the more commonly used agents produce prohibitive side effects or are ineffective or contraindicated

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Treatment of Hypertension Associated with Toxemia of Pregnancy

FRANK A FINNERTY JR

Georgetown University School of Medicine

Although the etiology and pathogenesis of toxemia are unknown clinical and laboratory experience attest to the fact that abnormal sodium retention and generalized vasoconstriction characterize the disease state Sodium retention which occurs in normal pregnancy seems by far the more important abnormality On the surface the consequences of sodium retention seem more serious than those following vasoconstriction (Fig 1) It should be stressed however that abnormal sodium retention precedes vasoconstriction and prevents the development of vasoconstriction

It follows then that the primary aim of therapy should be directed

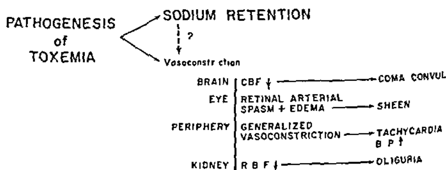


Fig 1

toward the prevention and correction of sodium retention Dietary restriction of sodium although effective is drastic on the patient and seldom practical Ammonium chloride has been found to be very effective in controlling the mild edematous states of pregnancy When the edema is of some magnitude necessitating the mobilization of significant amounts of sodium a satisfactory diuresis seldom follows ammonium chloride Our experience in this regard is in agreement with that of Assali who found that toxemic women show a decreased sensitivity to ammonium chloride When mercurials are used *in toxemia they usually produce a diuresis that is unsatisfactory and* that is seldom comparable to that following their use in congestive heart failure Recent renal biopsy studies show that the characteristic lesion of toxemia resembles nephritis Since these agents exert their effect by direct toxic action on renal tubular elements the mercurials should be contraindicated in toxemia

OUTPATIENT TREATMENT OF TOXEMIA

1 AT FIRST SIGN — EDEMA / B P / ALBUMINURIA

a CHLOROTHIAZIDE — 500 mg b i d
b REGULAR DIET

2 IF RESPONSE NOT SATISFACTORY ADD
a ACETAZOLAMIDE

3 IF B P MAJOR PROBLEM ADD
a RESERPINE — 0 25 — 0 5 mg h s
b HYDRALAZINE — 75 - 200 mg /day

Fig 2

Until recently acetazolamide (Diamox) was the drug of choice in the edematous states of pregnancy in our clinic The diuresis produced was frequently dramatic It was not unusual for example for an edematous pregnant patient to lose 4 to 5 pounds in a 24 hour period accompanied by clearing of the edema lowering of the arterial pressure and decrease in the albuminuria Continued administration for more than a month however was frequently accompanied by the development of drug resistance

Recently experience with chlorothiazide (Diuril) has shown that its diuretic effect is at least as potent as that of acetazolamide Its hypotensive effect is superior and probably most important it can be given continuously without the development of drug resistance

OUTPATIENT THERAPY OF TOXEMIA

This latter property of chlorothiazide has made it the most important single agent in the treatment and prevention of toxemia and edematous

states of pregnancy At the first sign of edema or elevation of arterial pressure or albuminuria (proved not to be pyelonephritis) chlorothiazide is administered in the dosage of 500 mg twice daily (Fig 2) The patient is allowed to enjoy a regular diet If in a week s time the response is not satisfactory (elimination or marked decrease of edema return of arterial pressure to normal and clearing of albuminuria) acetazolamide is added in a dosage of 250 mg twice daily every third or fourth day If the arterial pressure is a problem particularly if one is dealing with a patient with chronic hypertensive disease (history of hypertension prior to pregnancy) reserpine is added in a daily dosage of 0 25 mg If such a combination of chlorothiazide plus acetazolamide plus reserpine does not produce the desired effect and if the patient is not a candidate for hospitalization (see below) the addition of hydralazine (Apresoline) seems worth while Hydralazine therapy can be started with a dosage of 25 mg three or four times a day increasing the dose gradually to 250 to 300 mg per day Larger doses are never indicated in the pregnant patient since the therapeutic effect is seldom if ever increased and toxic reactions are frequent If the blood pressure response has not been entirely satisfactory at the end of two weeks hydralazine should be discontinued and hospitalization advised

INDICATIONS FOR HOSPITALIZATION

It is obvious that a severely toxemic or hypertensive pregnant patient should be hospitalized Difficult decisions arise however concerning the proper management of the patient with just a little toxemia who is seen in the seventh or eighth month of gestation How long should this patient be allowed to continue as an outpatient? When is an injustice being done by hospitalizing this patient and when is an injustice being done by not hospitalizing her?

We concur fully with Chesley and others who have convincingly demonstrated that the incidence of vascular damage following toxemia is proportionate not to the severity of the disease but to the duration of the toxemia Therefore if diuretic and antihypertensive therapy do not control the toxemic process in two weeks and if evidence of vasospasm (retinal vessels) and albuminuria are still present even though the diastolic pressure is lower and no edema is present more definitive hospital therapy is indicated From the long range standpoint it would seem that it is better to have a lot of toxemia for a short time than a little toxemia for a long time

It would also seem that once the stage of viability of the fetus has been reached there is no advantage in allowing a toxemic pregnancy to continue beyond two weeks if uncontrolled by therapy Since a patient with mild toxemia is not clinically sick and presents no immediate problem the seriousness of the disease is not fully recognized A conservative course is frequently decided upon in hope that the fetus will grow in size or at least mature In our experience once toxemia is present the fetus does not grow and each week the toxemic state is allowed to continue (even if manifested by only retinal edema and one plus albuminuria) the risk of vascular damage to the mother is increased

HOSPITAL THERAPY

For practical purposes the patients requiring hospitalization fall into

two groups the nonconvulsive and the convulsive The nonconvulsive group can be further divided into mild and severe

Mild Nonconvulsive In the mild nonconvulsive group a few hours of bed rest may be all that is necessary to control the toxemic process Chlorothiazide 1 gm a day and acetazolamide 500 mg a day are administered in conjunction with reserpine 2 5 mg administered every 12 hours intramuscularly

Severe Nonconvulsive The primary aim of therapy in severe toxemia is preparation of the patient for induction of labor or cesarean section Diuretic and antihypertensive agents in no way cure the toxemic process If a significant reduction in edema and vasospasm has not followed the diuretic and reserpine therapy in two hours or if the toxemic process is fulminating when the patient is first seen parenteral Veratrum is added to the regimen The average effective dose of Veratrum (Unitensen) is 0 25 mg in a reserpine and chlorothiazide treated patient The arterial pressure and heart rate are recorded at half hour intervals and the purified Veratrum is repeated whenever the arterial pressure is above 140/90 mm Hg Veratrum may be given as often as every hour if necessary If there is no hypotensive effect from 0 25 mg of purified Veratrum at the end of one hour the dosage is increased to 0 26 mg

Observation of the blood pressure chart and evaluation of the patient will soon inform the physician of the patient s sensitivity to Veratrum For example one may find that 0 25 mg of purified Veratrum will maintain a blood pressure under 140/90 mm Hg for three to six hours Veratrum is then repeated at three to six hour intervals as the case demands The amount and the dosage intervals vary from patient to patient without correlation with the initial height of the arterial pressure or the severity of the toxemic state The management of each patient therefore must be individualized

In the true hypertensive patient with a history of hypertension antedating pregnancy a reduction in arterial pressure to 140/90 mm Hg is neither practical nor necessary In this group of patients a level of 160/110 mm Hg might be used as an indication for additional Veratrum

One further point deserves mention After a hypotensive response has been obtained with Veratrum i e a blood pressure reduction from 160/110 to 130/70 mm Hg there is a temptation to repeat the dose at this normotensive level in the hope of prolonging the normotensive period Experience teaches however that Veratrum repeated at this level of arterial pressure does not prolong the normotensive period but only causes nausea and vomiting Veratrum should not be repeated therefore until the arterial pressure is at the beginning of the upswing

Although reserpine does not significantly enhance the hypotensive effect of Veratrum it more than doubles the duration of action The duration of the hypotension from the combined use of reserpine and Veratrum is in the range of eight to ten hours This prolongation of action permits less Veratrum to be used thus making the drug easier to administer more effective and less toxic The tranquilizing effect of reserpine and the hypotensive effect of Veratrum make for a particularly effective combination For practical purposes the premedication of reserpine to Veratrum therapy has done away with the nausea and vomiting usually accompanying Veratrum

An indwelling catheter is inserted on admission since accurate recording

of urinary output is essential Unless the patient is vomiting or dehydration is present intravenous fluids are not given In this regard the cases of congestive heart failure reported as complicating toxemia are actually induced by the overloading of the patient with fluids Just as intravenous fluids are *contraindicated in the presence of congestive heart failure or in acute nephritis* so also they should be contraindicated in cases of severe toxemia of pregnancy This is all the more true if there is oliguria or anuria

Once the blood pressure has been stabilized for eight to ten hours and a viable fetus is present induction of labor or cesarean section is advised The Veratrum routine is carried out through delivery or surgery and in the immediate postpartum period until the arterial pressure and heart rate have been stabilized

Convulsive Group Since convulsive toxemia of pregnancy is a medical emergency Veratrum is administered intravenously The purified form of the drug 1 0 mg is mixed with 20 cc of 5 per cent dextrose in water for intravenous use While the Veratrum is being mixed 100 mg of sodium pentobarbital is given intravenously immediately

With one physician recording the blood pressure every minute and another administering the medication (1) The Veratrum is given intravenously at a rate of 1 cc per minute until the first 20 mm Hg fall in systolic or diastolic pressure occurs (2) The needle is kept in place in the vein Additional Veratrum is not given for there will frequently be a precipitous drop in pressure in the subsequent one or two minutes (3) If after waiting one or two minutes no such reduction occurs Veratrum administration proceeds *at a rate of 1 cc per minute stopping at the first subsequent* sign of hypotension (4) If vomiting occurs 50 mg of pentobarbital sodium is administered intravenously (5) Next the needle is replaced with a sterile polyethylene plastic catheter inserted well into the vein A solution of 5 per cent dextrose in water is given through the catheter to insure patency All additional medication is given through this catheter

After the first hypotensive effect of Veratrum has been witnessed the *catheter being in place blood pressure recordings are made* at 15 minute intervals Additional Veratrum (one half the previous effective dose) is given whenever the blood pressure is 140/90 mm Hg or above Once again a few hours observation of the blood pressure chart and clinical appraisal of the patient will demonstrate the need for Veratrum at definite intervals such as every 40 minutes or every two hours the interval between injections becoming longer as the severity of the condition diminishes

Reserpine 2 5 mg is given *intramuscularly as soon as the convulsion* has been controlled and that dose is repeated every eight to 12 hours An indwelling catheter is inserted and an accurate record of urine output is kept The decision concerning the type of delivery is made entirely on the basis of obstetric indications

During labor and delivery regardless of technique there is no change in the Veratrum regimen The same routine is followed during the first 24 hours post partum or until the blood pressure has *become stabilized* and the signs and symptoms of toxemia have disappeared

Experience has shown that it is easier to prevent toxemia than to treat it The marked decrease in the incidence of toxemia throughout this country can be attributed mainly to restriction of sodium intake during the last half of pregnancy It is considered good obstetric practice in many centers to

restrict sodium routinely in the latter half of pregnancy particularly in the primigravida patient Our studies indicate that chlorothiazide is the ideal diuretic for the prevention of toxemia since long term continuous therapy is not associated with the development of drug resistance We feel therefore that chlorothiazide should not only be given at the first sign of toxemia but should also be instituted at the first prenatal visit of the hypertensive patient and the patient with chronic renal disease or anemia who is more susceptible to the development of toxemia

Addendum Preliminary experience with hydrochlorothiazide (Esidrex [Ciba] Hydrodiuril [Merck Sharpe & Dohme]) suggests that it is at least five to six times as potent as chlorothiazide which permits an average daily dose to be in the range of 100 to 200 mg Its diuretic and hypotensive action in the toxemias of pregnancy and its ability to potentiate the antihypertensive properties of other agents particularly hydralazine are equivalent to those of chlorothiazide

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The Treatment of Pyelonephritis, with Particular Emphasis on Hypertension

ELLARD M YOW AND TORU SAKUMA

Baylor University College of Medicine and Jefferson Davis Hospital Houston

Although there is no concrete evidence that pyelonephritis and hypertension are etiologically related the high incidence of the association of the two disorders and the less favorable prognosis of the hypertensive patient with pyelonephritis suggest strongly that the control of renal infection is an important objective in the management of hypertensive disease [1]

The extreme variations in the intensity and forms of therapy required to control infections in various parts of the urinary tract and with various anatomic complications emphasize the need for establishing an accurate and complete diagnosis in an individual patient Quantitative and qualitative urine cultures are helpful in separating infections of the kidney parenchyma

from those of other portions of the urinary tract and in determining which species are playing a significant role in the production of the infection Because of differences in safety with which different antibiotics can be administered and differences in their ability effectively to eradicate microorganisms the etiologic agent in each infection should be studied in the laboratory prior to beginning therapy An effort should be made to determine *in vitro* which antibacterial agent is merely suppressive and which has the greatest bactericidal effect against the specific strain producing the infection Appropriate diagnostic procedures should be carried out which will uncover the presence of foreign bodies and lesions interfering with the proper elimination of urine[2, 3, 4]

The control of the signs and symptoms of acute uncomplicated pyelonephritis is usually not difficult The study of serial biopsies of the kidney during therapy suggests that even in this form of pyelonephritis complete cure can best be attained by the administration of an antibiotic exerting a bactericidal effect against the causative organism (such as streptomycin polymyxin B kanamycin or penicillin) for a period of a week followed by therapy with a suppressive agent (such as tetracycline chloramphenicol or erythromycin) for an additional week

In chronic or recurrent pyelonephritis there is almost always an associated intra or extrarenal obstruction to urinary drainage In some instances the obstruction is due to the inflammatory reaction itself and in others there is a foreign body congenital defect cicatricial lesion or neurogenic disorder interfering with drainage When surgical correction of the obstruction is possible this should be carried out but when the obstructing lesion is the inflammatory reaction to the infectious agent the most intensive and prolonged medical therapy is required to control the infection permanently Patients with chronic pyelonephritis should be treated initially like those with acute pyelonephritis However more care should be given to the selection of the proper antibacterial agents and suppressive therapy should be continued until the maximum reduction of the inflammation has taken place This sometimes requires three to six months[6, 7]

No discussion of the treatment of pyelonephritis and its relationship to hypertension would be complete without a discussion of the relatively rare but important atrophic pyelonephritis Since Butler's earlier success[8] numerous contributions concerning unilateral atrophic pyelonephritis and its surgical treatment nephrectomy have been accumulated[9, 10, 11, 12, 13, 14] In sharp contrast to regular bilateral pyelonephritis atrophic pyelonephritis has a high incidence (47 per cent) of hypertension[10] Sensenbach[11] and Smith[13] made critical reviews in 1944 and 1956 independently With rigid criteria consisting of definite evidence of preoperative hypertension and postoperative blood pressure of below 140/90 for at least one year, Smith[13] found no remarkable improvement in the rate of successful restoration of normotension during the last eight years as compared with the results up to 1948 which had amounted to 26 per cent These figures are not completely reliable because of the inevitable fact that failures are prone to be unreported To reduce the number of failures and unnecessary surgical interventions that might aggravate hypertension Sensenbach[11] proposed four prerequisites (1) the diseased kidney should be functionless or its function greatly diminished (2) the opposite kidney should be functioning normally (3) the hypertension should be of short duration and (4) the younger the patients

age the better the outcome Braasch[10] discovered only 19 operable cases out of approximately 4000 hypertensives Although there is less than 0 5 per cent possibility of this condition being responsible for hypertension it must be borne in mind since it is the exclusive way to the permanent cure in selected cases

To summarize true pyelonephritis is a potentially serious disease requiring carefully planned and intensive treatment When anatomic defects are present and urinary drainage is altered these defects should be corrected The most effective antimicrobial therapeutic regimen in our experience has been to administer a bactericidal and bacteriostatic antibiotic concomitantly for 7 to 14 days followed by a continuation of the suppressive agent for a prolonged period of time The selection of the specific agents is dependent on the results of carefully performed *in vitro* sensitivity tests and the duration of the therapy is dependent on the chronicity of the infectious process

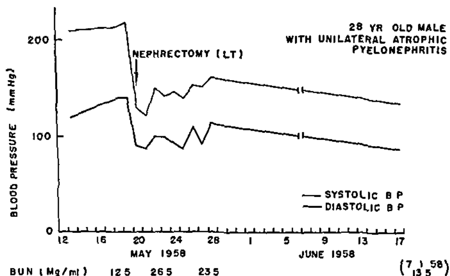


Fig 1 Patient with hypertension due to unilateral atrophic pyelonephritis Following nephrectomy there was a slow and progressive reduction of blood pressure to normotensive levels

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Surgical Treatment of Renal Hypertension

E F POUTASSE AND HARRIET P DUSTAN

Cleveland Clinic Foundation and the Frank E Bunts Educational Institute

Occlusive lesions of the renal artery or its major branches are now recognized as the most common remediable cause of renal hypertension At the present time the best means of diagnosis is renal angiography Between January 1 1955 and June 1 1958 256 hypertensive patients were selected for renal angiography 65 of these patients were found to have focal renal artery disease an incidence of 25 4 per cent Prior to 1955 six other patients were found to have focal renal artery occlusive disease and hypertension The lesions were found to be unilateral in 54 patients and bilateral in 17 The occlusive lesion was considered to be the primary cause of hypertension in the majority of patients but in some patients it was considered a complication of existing essential hypertension

The current indications for renal angiography in hypertensive patients are (1) disparity in length or excretory function of the kidneys as revealed by intravenous urography A difference of 1 cm or more in the lengths of the two kidneys of a hypertensive patient may represent renal atrophy a lag in the appearance of the radiographic media in one kidney especially on the five minute film would indicate a difference in excretory function (2) Hypertension in a patient less than 35 years of age in whom no other cause for hypertension has been discovered (3) Malignant hypertensive syndrome which develops in a patient over 55 years of age (4) Nonfamilial hypertension of recent onset in any patient with rapid progression into the malignant phase (5) Hypertension which develops or becomes worse following an attack of flank pain which may represent infarction of part of a kidney Most of the hypertensive patients studied between 1955 and 1958 fitted into these five groups

The purpose of this report is to outline the types of renal artery disease

found in 53 of the 71 patients and to discuss the results of surgical treatment in 47 patients Our earlier experience has been dealt with in more detail in a previous publication [1]

The roentgenographic findings of renal angiography were confirmed by operation or autopsy in 53 of the 71 hypertensive patients The majority of the renal artery occlusive lesions were arteriosclerotic plaques some of which had post stenotic aneurysms Nine patients had renal artery stenosis due to subintimal fibrosis or fibromuscular subintimal proliferation Renal artery thrombosis without other pathologic findings in the artery was found in five patients A small dissecting aneurysm of the renal artery was found in two patients

The effects of these lesions on the renal parenchyma are variable In a few patients no abnormality was found in others tubular atrophy ranged from minimal to severe and from focal to diffuse Complete occlusion of a branch of the main artery resulted in segmental renal infarction

Forty seven of 71 patients who had occlusive lesions demonstrated by renal angiography were selected for surgical treatment Severe retinal vascular disease was common among these 47 patients retinal hemorrhages and exudates with or without papilledema were observed in 27 Unilateral nephrectomy was performed in 30 patients segmental nephrectomy in 3 splenorenal arterial shunt in 2 aortic renal artery homografts in 5 excision of stenotic segment and repair of artery in 5 endarterectomy or dilatation in 2 The choice of surgical procedure depends upon the nature and location of the renal artery lesion whether the arterial disease is unilateral or bilateral the degree of atrophy in the involved kidney the severity of the patient s hypertensive cardiovascular disease and the versatility of the surgeon Nephrectomy is advised for unilateral renal artery disease when there is clear cut evidence of renal atrophy when the patient is too ill to withstand a prolonged surgical procedure or when the lesion is inaccessible to repair (orificial plaque) Segmental nephrectomy should be performed in those patients with lesions of a branch of the renal artery with or without renal infarction In patients with obstruction in the proximal portion of the left renal artery the lesion can be bypassed by removing the spleen and anastomosing the splenic artery to the distal healthy renal artery Stenotic lesions in the middle or distal portion of the renal artery can be excised and the artery repaired or endarterectomy performed Bilateral occlusive disease poses a formidable therapeutic problem When the lesions are orificial or in the proximal portion of the renal arteries a segmental aortic graft with bypass to the distal renal arteries has to be considered [3]

Of the 47 patients selected for surgical treatment 4 died within the immediate postoperative period—1 of myocardial infarction 1 of congestive failure 1 of hemorrhage from the site of an aortic renal homograft and 1 of a cerebrovascular accident Another patient died 2 months postoperatively having sustained extensive brain damage from a cerebral thrombosis on the third postoperative day Of the 42 patients who survived more than 2 months 5 have died all deaths were due either to complications of atherosclerosis or to progressive hypertensive disease

Of these 42 patients hypertension has remitted completely in 25 and 7 have only residual systolic hypertension In 4 patients blood pressure was somewhat lower after operation and in 6 it was unchanged This remission of diastolic hypertension occurred in 32 patients or in 75 per cent of those

treated surgically With return of diastolic blood pressure to normal all signs of *progressive arteriolar disease disappeared The patients with residual* systolic hypertension were all over 55 years of age this is not surprising since in the older age groups mild systolic hypertension is not unusual As concerns the 10 patients whose diastolic hypertension did not remit several points are worthy of consideration In the first place it is possible that arteriolar disease in the remaining kidney in some way allowed hypertension to persist Another possibility is that the localized arterial disease demon strated by angiography was merely a manifestation of premature atherosclerosis complicating essential hypertension It may be also that long standing hypertension changes the "set of the neurogenic vasomotor reflexes so that a hypertension once humorally mediated becomes neurogenically sustained this has been demonstrated to occur during the course of chronic renal hypertension in the dog[4] Finally it is possible that segmental arterial branches of the contralateral kidneys were the site of atherosclerotic lesions which were not recognized because of inadequate angiographic delineation

SUMMARY

The most common cause of remediable renal hypertension is occlusive disease of the renal artery or its major branches Of 256 hypertensive patients selected for renal angiography in a 3½ year period 65 (25 per cent) were found to have occlusive vascular lesions of one or both renal arteries

Seventy one hypertensive patients were found to have renal artery lesions as of June 1 1958 Forty seven were selected for surgical treatment 5 died within 2 months of operation Of the remaining 42 diastolic hypertension remitted in 32 in 4 blood pressure was somewhat reduced and in 6 it was unchanged

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Surgery in the Treatment of Hypertension of Adrenal and Renal Origin

REGINALD H SMITHWICK
Boston University School of Medicine

During the past 20 years I have operated upon approximately 2500 hypertensive patients One case in 56 was found to have hypertension of adrenal or renal origin Thus the cause of hypertension was known in only 1 8 per cent of patients No doubt some cases were overlooked, especially those having hypertension due to unilateral renal artery disease but even so the incidence of hypertension due to these causes is probably in the vicinity of 2 to 3 per cent

The great majority of these patients do very well especially if the diagnosis is made and operation is performed before secondary cardiovascular disease of consequence develops This important but small group of cases presents many interesting points for discussion perhaps the most important of these is the differential diagnosis In this brief presentation I shall confine my remarks largely to the problem of differentiating these patients from the much larger group of cases having so called essential or malignant hypertension, or in other words hypertension of unknown etiology

Table 1 summarizes my experience with these cases They are divided into four groups pheochromocytomas or paragangliomas hyperaldosteronism Cushing s syndrome and hypertension of renal origin

Twenty patients were found to have pheochromocytomas or paragangliomas They were pretty well scattered over the years 1942 to 1958 Pheochromocytomas or tumors arising in the medulla of the adrenal gland predominated 17 to 3 There is also an interesting preponderance of right sided tumors more than 2 to 1 There were no bilateral tumors in this series A few such cases have been reported in the literature

In six cases the hypertension was due to hyperaldosteronism Since Conn[1] first described this entity more than 100 patients having hypertension on this basis have been reported in the literature Four of our six cases were operated upon during the last three years Two additional cases operated upon in 1942 and in 1947 are included. Although this cause of hypertension was unknown at that time the clinical course of these patients following removal of cortical adenomas combined with microscopic evidence of hypokalemia in the kidney biopsy of one of these patients leads us to believe that they should be included in this category In the great majority of these patients a cortical adenoma may be found That was so in five of our six cases One patient had unilateral hyperplasia of the adrenal gland In four of the six cases the pathologic process was on the left side

By contrast in patients having Cushing s syndrome bilateral hyperplasia of the adrenal glands is the most common finding Occasionally a cortical

TABLE 1 HYPERTENSION OF ADRENAL AND RENAL ORIGIN (46 CASES)

1942	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58		
R	L				R	R	R		R	R	L P	R P	L P	R		R	Pheochromocytoma	(17)
R					R		R			R		R					or	
					L												Paraganglioma	(3)
					L												20 Cases	
					L												(R 14 L 6)	
R A					L A									R A	L A	L A	Hyperaldosteronism	(6)
																L H	Cortical Adenoma	(5)
																	Hyperplasia	(1)
																	(R 2 L 4)	
								H	H			B A	H	H			Cushing's	(7)
								H						L A			Hyperplasia	(5)
																	Cortical Adenoma	(2)
								L	R		L				R			
															R			
															R			
															R		Renal { Artery	(10)
																	} Parenchyma	(3)
															R		13 Cases	
															R		(R 9 L 4)	
															R			
															R			
															L			
															L			

adenoma is present as was the case in two of our seven patients In one of these tumors were present on both sides Occasionally the adrenal glands appear to be normal Unless an adenoma is found bilateral total adrenalectomy is the operation preferred by most surgeons

The hypertension was caused by unilateral renal disease in 13 cases As indicated by Table 1 the great majority of these patients were operated upon in 1957 10 of 13 cases This is due to the fact that helpful diagnostic tests have been developed in recent years The implication is that a good many cases of this sort have been overlooked in the past Two additional findings in this small series of 13 cases are that the main renal artery was *involved in ten and the right kidney was the culprit in nine* The patients we have operated upon for hypertension believed to be of unilateral renal origin in 1958 have not been included as the follow up period is short

DIFFERENTIAL DIAGNOSIS

With regard to differential diagnosis the problem is relatively simple in *Cushing s syndrome In the vast majority of cases the diagnosis is obvious* on clinical grounds The clinical appearance characterized by the round face buffalo hump pot belly muscle wasting thin skin and hirsutism leaves little doubt about the diagnosis The urine 11 oxycorticoids are almost always elevated while the 17 ketosteroids are often normal X ray evidence of demineralization of bone and a diabetic type glucose tolerance test are frequently present Sometimes clinical evidence of edema and low serum potassium and high CO are noted

THE PHENOMENON OF RELATIVE POSTURAL HYPOTENSION

We have found that evidence of postural hypotension in untreated hyper tensive patients should alert one to the possibility that the disorder may be caused by pheochromocytomas or paragangliomas hyperaldosteronism or renal disease When patients change from the horizontal to the upright position nine different effects on blood pressure can be observed These are summarized in Table 2 Only 26 per cent of patients with untreated essential hypertension in whom adrenal and renal abnormalities were excluded by surgical exploration (Table 3) had a fall in systolic pressure on standing combined with either a minimal rise in diastolic pressure (1 to 10 mm) no change in diastolic pressure or a fall in diastolic pressure By contrast 83 per cent of patients having hypertension due to one of these three causes had blood pressure responses of this sort on standing In most patients with essential hypertension both systolic and diastolic pressures rise on standing The phenomenon of relative postural hypotension is useful as a rough

TABLE 2 EFFECT OF STANDING ON BLOOD PRESSURE

1 S + D +	4 S 0 D +	7 S – D + { a (11 +) / b (1 to 10)
2 S + D 0	5 S 0 D 0	8 S – D 0
3 S + D –	6 S 0 D –	9 S – D –

After resting 15 minutes patient lying quiet environment
B P lying = Av 5 readings 1 minute intervals
B P standing = Av 5 readings 1 minute intervals

TABLE 3 INCIDENCE OF GREATER DEGREES OF POSTURAL HYPOTENSION AMONG

	100 Consecutive Hypertensive Patients Treated By Splanchnicectomy and Exploration of Adrenal Glands and Kidneys			35 Consecutive Cases of Hypertension of Adrenal or Renal Origin (Cushing's Excluded)		
DEGREE OF POSTURAL HYPOTENSION	NO CASES	PER CENT		NO CASES	PER CENT	
S − D + (1 to 10 mm)	14	14	26%	9	26	83%
S − D 0	1	1		3	8	
S − D −	11	11		17	49	

screening test because it is universally available inexpensive simple and painless Its presence is an indication to utilize the various more definitive diagnostic procedures which are now available

PHEOCHROMOCYTOMA OR PARAGANGLIOMA

In addition to the frequent presence of postural hypotension in untreated patients certain signs and symptoms should alert one to the possibility of this diagnosis These are summarized in Table 4 Increased excretion of urinary catechol amines is suggestive but may be present in patients with essential hypertension The same is true of a positive Regitine test The demonstration of a tumor by laminography is helpful as is displacement of the kidney downward and outward Less desirable tests are perirenal air injection (not without hazard) or the precipitation of an attack with histamine (not without risk) In the great majority of cases the diagnosis can be made but since there is no absolutely certain diagnostic procedure surgical exploration will have to be resorted to occasionally To be emphasized is the fact that the majority of patients do not have paroxysmal attacks

TABLE 4 HYPERTENSION DUE TO PHEOCHROMOCYTOMA SHOULD BE SUSPECTED IN THE PRESENCE OF ANY OF THE FOLLOWING SYMPTOMS OR SIGNS

1 Excessive sweating
2 Vasomotor phenomena
3 Elevated temperature
4 Normal cold pressor response
5 Blood sugar 120 or more
6 B M R + 20 or more
7 Postural tachycardia
8 Postural hypotension
9 Glycosuria
10 Paroxysmal attacks

HYPERALDOSTERONISM

Since persistent hypokalemia is invariably present that is a serum potassium of less than 3 7 it is essential that every patient with hypertension be screened as to serum potassium level In this disorder there is also an increased excretion of potassium in the urine (730 milliequivalents/day) when the serum K is low The plasma CO_2 is elevated and the specific gravity of the urine is usually low The urine pH tends to be high There may be a history of polyuria or muscle weakness What may prove to be an essential

diagnostic feature is an increase in the excretion of potassium in the urine with a further lowering of serum potassium when the sodium chloride intake is increased to 150 to 200 milliequivalents/day Urine aldosterone may be normal or increased Postural hypotension has been present in the majority of our cases The laboratory findings referred to above are so clear cut that it seems as if this diagnosis can be made with great accuracy

HYPERTENSION OF UNILATERAL RENAL ORIGIN

In our experience as well as in that of others this diagnosis has been made much more frequently during the past two or three years In this connection we have found the presence of postural hypotension which has been present in most of our cases to be a very helpful hint especially when the intravenous pyelogram has been normal We have also found the Howard test[3] to be of great value as a definitive test particularly when the intravenous pyelogram is normal So far there have been no false negative or positive tests in our series In patients who show little or no function in one kidney by intravenous pyelography the test has been unsatisfactory and it is probably not worth doing under these circumstances

More recently we have been using the radioactive Diodrast clearance test as a screening test in all hypertensive patients To date there have been no false negatives and we are enthusiastic about it Because of its apparent value as a screening test for relative unilateral renal disease or bilateral depression of renal function I am describing the test briefly

Radioactive Diodrast Clearance Test The use of radioactive Diodrast in the study of renal function was first employed by Winter[4] More recently Block Burrows and Hine[5] have described a modification in technique utilizing I^{131} labeled Diodrast and "carrier Diodrast with external monitoring over the renal areas as a screening procedure for unilateral renal disease Well hydrated patients were seated upright with the kidney monitors directed horizontally at the renal areas normal to the skin surface An intravenous infusion of 300 cubic centimeters of 5 per cent dextrose in distilled water containing 3 cubic centimeters of 35 per cent Diodrast solution was administered at a rate of 2 cubic centimeters per minute Two and one half cubic centimeters of 35 per cent Diodrast solution was injected directly into the rubber tubing of the infusion apparatus as a "liver blocking" dose Immediately thereafter 20 microcuries of I^{131} labeled Diodrast (approximately 0 1 mg) was similarly injected and graphic recordings were obtained as follows (1) a direct tracing of the counting rate in one renal area and (2) the ratio of the radioactivity in one renal area to *the total radioactivity* in both renal areas Information regarding renal function of one kidney is obtained from the direct kidney recording Inspection of the ratiometer recording provides a comparison of renal function in the two kidneys The tracings were carried out for 30 minutes at which time a urine sample was collected in order to calculate the percentage of the injected dose of I^{131} Diodrast excreted during that period *of time*

A more recent summary of the observations made by Block and Burrows[6] in a series of hypertensive patients using this method indicates that this test is a rapid painless accurate and safe way to screen hypertensive *patients* for abnormalities in renal function What can be learned from this test may be summarized as follows

1 Negative—rules out relative unilateral renal disease
2 Positive—indicative of relative unilateral renal disease which may be the cause of hypertension
3 Not by itself an indication for nephrectomy or direct surgery of the renal artery
4 A valuable screening procedure particularly in detecting an ischemic kidney if the intravenous pyelogram is normal
5 Detects bilateral depression of renal function

An example of a normal test is illustrated by Figure 1 In patients with hypertension of unilateral renal origin there are usually both diminished uptake and delayed excretion of the test material by the affected kidney An example of renal hypertension with such a tracing is illustrated by Fig

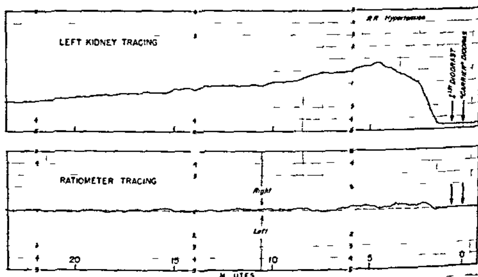


Fig 1 Radioactive Diodrast clearance test This figure depicts the I^{131} Diodrast technique of Burrows and Block The upper portion shows the uptake and excretion of I^{131} Diodrast by one kidney in this instance the left In the lower portion the ratiometer tracing indicates any difference there may be in uptake or excretion by the two kidneys In this instance there was none

ure 2 Other confirmatory data in this case include a short history of severe and rapidly progressive hypertension in a 50 year old male postural hypotension a positive Howard test the finding of an infarcted upper pole of one kidney due to thrombosis of a branch of the right renal artery and a dramatic blood pressure reduction following nephrectomy

Some have made extensive use of aortography not only as a definitive diagnostic procedure but as a screening test as well[7] Since this maneuver is not without serious morbidity and even can have fatal consequences we avoid it whenever possible Since the diagnosis can now be made without it we rarely use it It can be helpful in deciding about a rare case of bilaterally depressed renal function when one wonders about the possibility of bilateral renal artery disease which might be amenable to a direct surgical approach When it is a question of hypertension of unilateral renal origin we never use it unless surgical exploration is equivocal Then we do it at the time of operation and occlude the good renal artery injecting 10 cc of 50

per cent dye near the questionable renal artery occluding the aorta distally Every patient who has had an aortogram so far with hypertension of unilateral renal origin has had nitrogen retention and oliguria for a period of 10 days ± when the dye was permitted to enter the good kidney Fortunately this complication has not as yet proved fatal We hope to avoid it in the future

In critically ill patients with encephalopathy or other serious complications of hypertension of unilateral renal origin it is wiser to do a nephrectomy than to attempt to correct unilateral renal artery disease The latter is a procedure of far greater magnitude and the late results of direct surgery

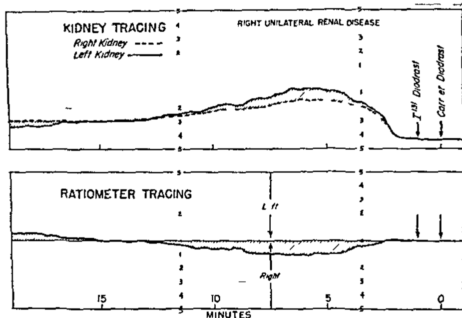


Fig 2 Radiactive Diodrast clearance test This figure illustrates a relative decrease in both uptake and excretion of I[131] Diodrast by the right kidney The uppermost curve shows the uptake and excretion by the left kidney (solid line) The shaded area in the ratiometer tracing below indicates that there is a difference in uptake and excretion of I[131] Diodrast by the two kidneys When this is applied to the upper curve the shaded area between the solid and dotted lines means that the function of the right kidney is relatively defective in both uptake and excretion of I Diodrast This suggests hypertension of unilateral renal origin

are yet to be evaluated A living patient with one good kidney is preferable to a dead patient with potentially restored circulation to a relatively ischemic kidney

SUMMARY

1 As indicated by this brief discussion hypertension of known etiology represents only about 2 to 3 per cent of the total number of cases today If the diagnosis is made before serious cardiovascular damage occurs the outlook is good after the causative mechanism is corrected surgically The differential diagnosis is therefore of primary importance

2 At this time the necessary criteria are available so that the diagnosis of Cushing's syndrome hyperaldosteronism and hypertension of unilateral renal origin should rarely if ever be missed The great majority of cases of hypertension due to pheochromocytoma or paraganglioma can be detected Surgical exploration is still occasionally necessary to establish the diagnosis

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Discussion

CARL F SCHMIDT *Moderator*

JOHN BEEM	CHARLES HEIDER
ALBERT BRUST	WILLIAM HOLLANDER
WILLIAM DAESCHNER	SIBLEY HOOBLER
HARRIET DUSTAN	JOHN HOWARD
FRANK A FINNERTY	WILLIAM PATON
RALPH FORD	HENRY SCHROEDER
EDWARD FREIS	REGINALD SMITHWICK
RAY GIFFORD	ELLARD YOW
ARTHUR GROLLMAN	

DR SCHMIDT At what potassium serum level is supplementation of the intake of potassium indicated?

DR FREIS We are now giving supplementary potassium when the serum potassium level is below 3 5 milliequivalents per liter and we are using Potassium Triplex which is a proprietary elixir of potassium salts We use a dose of 50 to 100 milliequivalents per day

DR GIFFORD I have not been giving supplementary potassium until the serum potassium concentration drops below 3 mEq /L We have many pa

tients whose serum potassium has varied between 3 and 4 mEq/L who have not received supplementary potassium and they have not experienced any symptoms This indicates that most patients can get along without supplementary potassium in their diet unless they become acutely ill with a febrile illness with nausea and vomiting or have an operation Then sometimes these patients develop clinical manifestations of the hypokalemia If they don t have an avenue of excess potassium loss or if their diet is adequate most of them have no symptoms from this degree of hypokalemia We found that supplements in the order of 50 milliequivalents a day did not prevent hypokalemia nor did it correct hypokalemia when it was present in about a third of the patients Now we advocate the use of about 100 milliequivalents per day

DR SCHMIDT A question has been presented to me stating that there are people who on prolonged use of chlorothiazide develop an increase in total exchangeable sodium and it is thought that sodium goes into the cells to replace potassium loss Do these people under this set of circumstances have characteristic electrocardiographic changes?

DR FREIS No We found a very poor correlation between the reductions in serum potassium and electrocardiographic changes They don t show changes in their electrocardiograms such as one would expect to see in hypokalemia of a severe degree Neither do they have muscular weakness They feel very well

DR DAESCHNER The serum potassium concentration is a relatively insensitive method for determining total body potassium deficits and serum potassium concentration may well be normal in the presence of quite significant total body deficits Probably the bicarbonate content of plasma or the total CO is a more sensitive method of suggesting early evidence of alkalosis Since potassium is a relatively nontoxic substance when given by mouth it seems reasonable to me to use it as a supplement whenever the possible development of potassium deficit is likely

DR HOLLANDER I disagree somewhat with the statements made The level of serum potassium is a good index of total exchangeable body potassium We have correlated changes in body potassium with serum potassium using balance studies In general when about 100 milliequivalents of potassium are lost from the body then the serum potassium will begin to fall I don t think there s a good correlation between the carbon dioxide content of the blood and the total body potassium

DR SCHMIDT In some of the data presented during this symposium cases were shown in which the blood pressure readings obtained by the physician were very high when compared with those obtained on the patient at home by someone else Was the diagnosis of hypertension justified in these patients when the original blood pressure was taken by the physician and not by the patient s family?

DR. SCHROEDER That is an excellent question I think it means that in order to make a diagnosis one has to screen the patient very carefully and get the blood pressure taken by somebody else For a number of years I have not

taken a blood pressure except for my own amusement I prefer to have nurses take it because I think that this is a much more valid indication of what the blood pressure is than when I take it myself I think that in the hospital as Dr Smithwick pointed out many years ago you re more apt to get a true reading or a relatively truer reading with the patient at rest using these levels as controls anyone can determine the effect of therapy

Dr Smithwick Some of you may remember some of the articles that Dr David Ahman wrote on this subject He made a very extensive study of the differences between clinic and home blood pressure readings 20 years or more ago He would frequently have six months of daily clinic blood pressure readings prior to doing a sympathectomy and then along with these he had daily blood pressure readings taken by the patient himself or a member of the family There isn t any question about the fact that such data, if properly gathered are highly significant You can have a very striking effect on blood pressure levels on the basis of home blood pressure readings following treatment of one sort or another when there is essentially no demonstrable difference on the basis of observations made in the clinic on ambulatory patients

Dr Gifford There are other signs of hypertensive disease besides the level of the blood pressure It s true that in the physician s office the blood pressure may be unusually high In that situation the elevation of the retinal findings the degree of arterial narrowing and focal constrictions in the retinal vessels are important Cardiac signs and the electrocardiograms are also significant If you see patients with exceedingly high blood pressure in the office with almost no changes in the retinal arterioles with normal heart size with a normal electrocardiogram and nothing to indicate diffuse vascular disease of hypertension these are the patients who deserve study to find out just how artificial the elevation was that you got in the office Then it is a good time to put them in a quiet room in the hospital to see what happens to the blood pressure

Dr Freis I hope that some of the people don t interpret this to mean that all you have to do is have your office nurse take the blood pressure instead of the physician Actually the office nurse will often get high pressures too Time is another phase of this and if you re going to depend on a clinic or an office pressure the patient should be there just about the whole day On the type of patient that Dr Gifford is talking about I prefer to give him two weeks with blood pressure readings at home Frequently you will see it drift down over three or four days rather than falling immediately when he gets home

Dr Schroeder In a study of several hundred patients examined by at least three different physicians myself being one of them the decision was made that the patients had hypertension which was severe enough to require ganglionic blocking agents The patients were then admitted to the hospital We were wrong in a little over 10 per cent of patients referred to us In other words when the patient got into the hospital and the nurses took the pressure the next morning there was nothing to treat the pressure was normal

DR FINNERTY Should such a concept state then that when one evaluates the severity of the vascular disease the least important thing is the blood pressure?

DR HOOBLER The blood pressure is important if it continues to be elevated in the home in the absence of vascular disease What Dr Freis said is exactly right No reading in the office is really the representative one but a reading day in and day out at home I think is a truly representative one Dr Gifford made the comment that very often before you embark on treatment a period of home readings is a very wise way to evaluate where you stand Under these circumstances (home readings) the blood pressure elevation as such is a very important consideration

DR SMITHWICK I ve always found that it was essential to satisfy yourself that the patient really had hypertension before you instituted treatment And of course we ve always tried to get blood pressures taken by a carefully trained technician so that we did not rely on different physicians We have a system that we use We get pressures on the ambulatory patients and then we get hospital bed rest readings There are certain individuals who are born with unusually variable blood pressures within the normal range Then as they get older their blood pressures get out of the normal range and if they go to see a doctor or try to get some life insurance or something their pressure is elevated When you put them at bed rest the blood pressure goes right down to normal Those patients are in the phase of so called intermittent hypertension They don t have continued hypertension and if you treat patients of that sort with drugs or by operating on them you re just kidding yourself as to what the results are You ve got to prove that your patient has continued hypertension before you say that he has hypertensive vascular disease It s terribly important to take that into consideration when evaluating therapy What Dr Gifford said is also true—that it is not until the patient has developed continued hypertension that he begins to show cardiovascular changes Occasionally you ll see a person in the stage of intermittent hypertension who has retinal hemorrhages or an enlarged heart or an abnormal electrocardiogram or something of that sort but it s invariably a male and it is very rare It isn t until the patient develops continued elevation of diastolic blood pressure at bed rest that he really begins to get into trouble

DR FORD I wonder if we could label the subject that we are now discussing "stress in hypertension" and then I hope without making us turn 180 degrees label it hypertension as related to the adrenal gland" and then to ask two questions If we take the heterogenous population of hypertensive patients beneath the age of 55 with BUN s less than 40 what would be the frequency of abnormal adrenal function as a cause of these patients hypertension? The second question is Should we not be looking for certain borderline cases of Cushing s syndrome (or we might label it functional hypercorticism) in all of our hypertensive patients? In short the two questions I would like to have answered are What is the frequency of a significant adrenal factor other than pheochromocytoma in the heterogenous population beneath the age of 55 with normal or essentially normal renal function?

DR SCHMIDT In patients who are on ganglion blocking agents are better end results obtained by raising the head of the bed to a slight degree during sleeping periods?

DR DUSTAN Patients vary in the angle at which they start to get an ortho static reduction in blood pressure It may be helpful in the occasional pa tient but as a general rule I think its prime helpfulness is for the physician who feels that he is doing everything he can for the patient

DR FORD This procedure is often quite helpful in relieving hypertensive headache Even though the systemic blood pressure may not decrease sig nificantly the intravascular and tissue pressures in the brain are reduced enough to prevent hypertensive headaches in many patients thus treated

DR SCHMIDT Since exercise is a good vasodilating agent is exercise stressed in the management of moderately severe essential hypertension? Are patients who work hard manually with moderately severe hypertension likely to die from myocardial infarction or from cerebral vascular disease?

DR FREIS It s been shown that in patients who are taking ganglion block ing agents the effect of exercise is to lower rather than to elevate blood pressure Although exercise does dilate muscle vessels the net over all effect is an increase in blood pressure in the average normal person which is mostly a systolic pressure increase But with the use of ganglion blocking agents interestingly enough blood pressure often decreases rather than rises with exercise

DR SCHMIDT One of the responses here is that cardiac output is likely to increase greatly during exercise in the untreated patient isn t it as well as fluid shifts?

DR FREIS Yes and the ganglion blocker prevents the increase in cardiac output by pooling blood peripherally

DR GIFFORD I don t think we should imply that exercise even though it should raise blood pressure temporarily is particularly harmful in the man agement of patients with hypertension Unless there is some other reason such as coronary artery disease or congestive heart failure I don t ordinarily restrict the physical activities of my patients whether they are on ganglion blockers or not

DR SCHMIDT Are patients who do hard manual work with moderately severe hypertension likely to die from myocardial infarction or from cerebral vascular disease?

DR DUSTAN Any patient with prolonged hypertension is likely to die from either of those I m not sure what role exercise plays in it

DR HEIDER The importance of frequent periods of rest and relaxation cannot be overestimated Recreational exercise suited to the age and condi tion of the patient is essential On the contrary it is just as essential that

periods of excessive physical and mental fatigue be avoided The exercise program must be individualized for the patient

Sedative drugs such as phenobarbital meprobamate bromides and the host of other so called tranquilizers" are no substitute for an intelligent systematic and well planned way of life for the patient Ambulatory patients with severe hypertension obtain only slightly more blood pressure response to sedatives than to completely inert placebos

DR SCHMIDT Of what value is psychotherapy in treating hypertension?

DR HEIDER Patients with hypertension require an understanding and sympathetic therapist If the patient is to gain maximum benefit from treatment the therapist should have a complete understanding of the disease and above all he should know the pharmacology of the drugs he is using so that he can employ them with confidence and determination rather than fear and trepidation At the same time he must understand their limitations and side reactions so that the welfare of the patient is not jeopardized

In our experience it is indecision and a feeling of futility on the part of the therapist that lead to fear on the part of the patient This increases his anxiety and concern for his future both of which aggravate the hypertension It is much better to approach the patient with a frank and honest appraisal of his condition than to foster a state of suspicion and confusion which results when an attitude of secrecy is adopted by the therapist

If the patient has mild and labile diastolic hypertension without evidence of renal disease he should be apprised of his condition especially if he is a younger individual below the age of 40 He should be informed that his prognosis is no worse than that of normotensives of the same age group just as long as the hypertension does not progress However this means that for insurance against progression the patient must be advised to take certain precautions These include regular return visits to his physician and steps if possible to eradicate periods of severe stress both in his domestic life as well as in his occupation This takes time thought and effort on the part of the therapist It is not enough to say Stop worrying and come back to see me in six months"

When the disease is severe enough to require antihypertensive drugs the therapist should not hesitate to use them and their use should be approached with confidence but due alertness for untoward side effects The instructions for use of the drugs must be clear and concise The patient should be informed that with adequate but continued drug therapy there is no reason to believe that he cannot be made normotensive and that he will do as well as any normotensive person of his age and general physical status The patient should be apprised of possible untoward side effects of the drugs as a precautionary measure but this should be done without conveying an attitude of fear and apprehension Otherwise the patient again fears the unknown develops anxiety and loses faith in both the drugs and the therapist *He will frequently become frightened and stop taking* the drugs at the slightest excuse often seeking out another physician

DR SCHMIDT Of what importance is obesity?

DR HEIDER Obesity is frequently associated with hypertension the obese individual especially is likely to have mild hypertension On the contrary

in our clinics the incidence of severe hypertension is no greater in obese patients than in the thin asthenic individual There is no evidence that obesity will produce diastolic hypertension of the severe and incapacitating type Nevertheless if weight reduction can be undertaken usually it will be beneficial Some reduction in blood pressure is frequently observed and loss of weight can be expected to ease the strain on the overtaxed cardiovascular system There is a practical aspect to the problem in that weight reduction is prescribed many many times but is rarely successful for sustained periods of time Dextro amphetamine (Dexedrine) may make the job of reducing food intake a bit easier and in a study conducted in our clinic there was no evidence that this drug aggravated the hypertension

DR SCHMIDT Is smoking contraindicated in hypertensive patients?

DR HEIDER Smoking frequently aggravates hypertension since nicotine stimulates sympathetic ganglia as well as the neurogenic synapses within the central nervous system Therefore when the habit can be dispensed with without excessive psychic trauma it should be done But some patients have become so dependent on the smoking habit that the anxiety and psychic effect produced by discontinuing smoking would far outweigh the benefits It becomes an individual problem and the therapist and the patient together must make the decision

DR SCHMIDT The next question is Will you please poll the panelists in regard to the current status of surgical sympathectomy at their respective institutions? Specifically which hypertensive patients are surgically sympathectomized at institutions other than Dr Smithwick s?"

DR SCHROEDER I m sitting next to Dr Smithwick but I am not going to modify my answer I think the patient who is uncooperative on drug therapy but who requires effective treatment should be sympathectomized The patient who prefers sympathectomy to taking pills should be sympathectomized And the patient who becomes resistant to drug therapy should be sympathectomized Now in those three groups I think it s essential that we urge sympathectomy unless of course they are azotemic

DR HOOBLER I would agree completely with that point of view In our institution we follow the policy that sympathectomy is indicated in those patients who are having a hard time on drugs and need therapy because of severe hypertension I tend to encourage sympathectomy because I feel we see more and more good results with the use of drugs given to patients who had a sympathectomy previously

DR HOLLANDER This goes for the young patient especially the male who does not have a brilliant response to antihypertensive drugs These patients should be considered for sympathectomy

DR FREIS One other point probably should be mentioned that is that you don t commit the patient quite as badly as you used to when you recommend a sympathectomy because many of your patients who do not respond to sympathectomy or lose their initial nice antihypertensive response

to sympathectomy can be treated effectively by giving them chlorothiazide Sympathectomy followed by chlorothiazide is a very simple regimen With cholorothiazide you can now turn most of the failures of sympathectomy into successes I wonder whether Dr Smithwick agrees with that

DR SMITHWICK There is a very definite place for sympathectomy I would agree with what has been said so far that sympathectomy is indicated in patients who won t respond to medical treatment or who cannot or will not follow it or in whom even if it is successful the side effects are upsetting especially in the young individuals in the twenties and thirties with really severe hypertension I think that forty or fifty years is a long time to take large doses of pills it is an awful lot to put the patient through when he can have a very conservative sympathectomy in our day I have been doing less and less radical sympathectomies We do them in one stage with little or no disability resulting compared with the radical operations we used to do And as Dr Freis has said the patients are very responsive to the milder antihypertensive drugs and it looks as though you can control them indefinitely A lot of these people won t continue to take the drugs but the sympathectomy alone gives them a certain amount of continuous protection I noticed in one paper this afternoon that nearly half of the patients that were used as control subjects for drug treated patients failed to follow the treatment I think that this is an important point

DR FINNERTY There is one other group of patients that should be mentioned This is the group of women with severe hypertensive disease who are desirous of having a family If these women are sympathectomized and then are followed closely while pregnant and put on a good salt free regimen this is a way that they can have a family without severe jeopardy to their lives The second group of patients that should be sympathectomized consists of those people whose blood pressures are significantly higher when they stand particularly if they are employed in a standing job such as someone who works in a laundry They might particularly benefit by sympathectomy

DR SMITHWICK The latter is a very interesting point Over the years we ve always studied the blood pressure while the patient was both lying and standing There are about 20 per cent of hypertensive patients who have significant rises in diastolic pressure when they stand Sometimes the diastolic pressure rises as much as 50 mm of mercury over the horizontal level They are the ones who really do beautifully with a sympathectomy

DR HOOBLER How about the prognosis in the young boy who wants to avoid impotence? This is a problem of course with any ganglion blocking therapy and a fairly common experience with chlorothiazide alone I wonder whether Dr Smithwick can avoid this problem by the type of sympathectomy he does Would you elaborate a little on that?

DR SMITHWICK Well that can be avoided without any question If you do the type of splanchnicectomy that is a little more extensive than what Dr Peet originally described that is a little more extensive in an upward direction and if you don t remove the sympathetics below T 12 the patient will never be impotent or sterile I believe that with these newer hypotensive

drugs all you need to do is remove from lumbar 8 to lumbar 12 on both sides and that gives you very little postural hypotension even in the acutely denervated state It is a mistake to do too radical an operation now because if you are going to add drugs to it then you get into the difficulty of intensifying postural hypotension It is much better to do the most conservative type of splanchnicectomy and concede that in a large percentage of the patients you are going to supplement it with a relatively simple medical regimen I believe that a great majority of the very young people get along well that way

Dr Hoobler The reason I asked that question was because I believed just what you have said Then we advised one young man to have such a limited sympathectomy Postoperatively he was impotent I wonder how frequently it occurs with a D 8 to D 12 sympathectomy In your experience is it very common?

Dr Smithwick No not with a limited splanchnicectomy

Dr Gifford I would like to add one discordant note here and I hesitate to do so because I know I am the only one who has had this experience Out of seven patients who had persistent hypertension after sympathectomy in our series only two responded to chlorothiazide with sufficient reduction in blood pressure that we could maintain them without adding more potent compounds to the therapeutic program

Dr Schmidt Dr Hollander when adequate doses of mercurial diuretics are given to produce the same amount of natriuresis as that produced by chlorothiazide is there a similar effect on blood pressure? If so what are the implications as to dynamics?

Dr Hollander Yes parenteral mercurial diuretics have a similar effect on the blood pressure as chlorothiazide and as pointed out earlier mercurial diuretics like chlorothiazide do not lower blood pressure in normal individuals I don t know what this means

Dr Schmidt Dr Finnerty how does blood pressure reduction alter mortality in the infant and/or mother? Does the blood pressure response to specific acute hypertension in toxemia shed any light on etiologic factors?

Dr Finnerty I will answer the second question first Certainly the toxemic process is most sensitive to salt depletion Whether this is due to the fact that the toxemic process is associated with acute glomerular disease or not I don t know It is our clinical impression that acute glomerular disease is more sensitive to sodium depletion than is say nephrosclerosis

The first part of the question was how does blood pressure reduction affect mortality in the infant and/or the mother? In eclampsia, the infant mortality of most nontreated series is about 90 per cent In the treated series, and it doesn t make much difference what treatment as long as the blood pressure is reduced effectively the mortality can be reduced to 45 per cent but you see it is still very significant In the nonconvulsive toxemias the mortality of the infant is in the neighborhood of 50 to 55 per cent and in effectively treated patients this can be reduced to 10 per cent

DR SCHMIDT Dr Dustan what happens to patients three years postoperatively when they are operated upon for renal arterial occlusive disease? Does arteriosclerosis progress?

DR DUSTAN I don t know what happens to very many people three years postoperatively because we haven t followed our patients that long I know that arteriosclerosis certainly progresses in the face of normotension and that since many of these people have arteriosclerosis as the basis of their hypertension and since we don t know what is the cause of arteriosclerosis and don t have any idea how to treat it we have every reason to suspect that this just goes on uninhibited except perhaps that the progress is slowed a little bit by the lowering of the blood pressure

DR SCHMIDT Have blood dyscrasias been observed with the use of chlorothiazide?

DR HOOBLER I have a definitely documented case of chlorothiazide producing thrombocytopenia When the drug was discontinued the thrombocytopenia improved the drug was given again and the thrombocytopenia recurred Just one case out of many hundreds certainly doesn t condemn the drug but it is something we should know about

DR GIFFORD I would like to add to that We have had one case of thrombocytopenia without purpura two cases of purpura without thrombocytopenia and one case of anemia as the result of the administration of chlorothiazide in over 500 patients treated with the drug

DR SCHMIDT Does tolerance develop to the hypotensive effect of chlorothiazide?

DR HOOBLER I would say that there are certainly cardiacs who continue to have edema on chronic doses of chlorothiazide and this can be relieved often by hydrochlorothiazide Also I think some cardiacs manage better on intermittent doses when their weight goes up rather than running the risk of tolerance by giving it continuously You have to select your patients

DR SCHROEDER May I ask a question about chlorothiazide? I got the impression that this drug used alone is a pretty good drug for hypertension I would like to ask Dr Hollander Dr Hoobler Dr Freis and Dr Grollman how many times have you seen chlorothiazide used alone without a low salt diet produce normal blood pressure in grade III or grade IV hypertensives?

DR FREIS If I gave you that impression I am sorry since this is not the impression I meant to convey I said that the reduction of blood pressure occurred in only a certain number of hypertensives who were not getting other agents and that it was a very modest reduction about 15 per cent Of course the original papers on chlorothiazide pointed out that its main action was to enhance the antihypertensive effects of other drugs but it is of great *theoretical* interest in regard to hypertension that there are some hypertensives who show a definite although modest reduction of blood pressure

DR FINNERTY We have studied 16 patients now with severe grade III and grade IV fundi with chlorothiazide as the sole treatment for six months and we certainly are sorry we started the study because they have all gotten worse

DR HOOBLER We wouldn t put the patients with very severe disease on chlorothiazide alone and we haven t seen them get normotensive I can think of two patients though who would fall into early group III who are now nearly normotensive on chlorothiazide alone Their blood pressures are 150/100 using their home blood pressure readings I would say that in a young patient with milder hypertensive disease we do see drops I didn t mean to give the impression that this is the sole drug but it is a useful one It is worth persevering with in the hope that your patient will be one of those who respond when you can afford to temporize for three to four months

DR PATON May I ask Dr Freis whether these patients sensitive to chloro thiazide are sensitive to other drugs too or not?

DR FREIS I am sorry I don t know the answer to that

DR PATON I wonder if they really are so unusual as to be so important

DR FREIS Well they represent a very interesting group that is the ones who are sensitive to chlorothiazide and we are certainly going to see if they are any different from other kinds of hypertensives

DR SCHROEDER Would they be sensitive to low salt diets?

DR FREIS I would imagine they would Dr Schroeder yes These are the people who would have a nice response to low salt diet

DR FORD May I ask a question concerning the relative antihypertensive potency of hydrochlorothiazide and chlorothiazide? I believe that Dr Hol lander presented some data earlier today on the relative antihypertensive potency of hydrochlorothiazide compared to chlorothiazide which was not clear to me

DR HOLLANDER The average dose of chlorothiazide in the study was 750 mg a day The average daily dose of hydrochlorothiazide was 75 mg per day The range of dosage of hydrochlorothiazide was 37 5 mg to 100 mg We also have studied seven subjects on a daily dosage of hydrochlorothia zide of 150 mg but we haven t compared the results in those patients with a dosage of chlorothiazide ten times that When you give a dose of 150 mg of hydrochlorothiazide you will get a more effective reduction in the blood pres sure than with chlorothiazide At the same time you will produce many more disturbances in the blood chemistry including reduction of serum potassium and an elevation in the blood urea nitrogen It would seem that 150 mg of hydrochlorothiazide would be the maximal dose and the minimal dose is probably about 37 5 mg per day the average dose being about 75 mg a day

DR FORD Is hydrochlorothiazide more potent aside from the difference milligram for milligram? What are the differences in the characteristics of the dose response curves of these two agents?

DR. HOLLANDER Our results indicate that hydrochlorothiazide in one tenth the dose of chlorothiazide is slightly more effective than chlorothiazide I would also say this however that initially our results obtained with chloro thiazide are considerably better than the results that we have obtained with prolonged treatment with chlorothiazide

DR FREIS Our dose response curves would indicate that hydrochloro thiazide is about 12 times more potent than chlorothiazide

DR FORD You re just comparing milligram for milligram doses not maxi mum responses with each compound?

DR FREIS Yes thats right

DR FORD That doesn t mean necessarily that it s any more potent I mean does the drug produce a greater increase in sodium excretion with higher doses?

DR FREIS No I don t think the two drugs are qualitatively different at all I think that it s only a matter of dosage difference

DR HOLLANDER Dr Freis it appears from what you have said that the average dose of hydrochlorothiazide should be 75 mg a day In view of your average dose of chlorothiazide 1000 mg a day we are in a pretty good agreement aren t we?

DR. SCHMIDT What advantage if any does the new diuretic hydrochloro thiazide offer over chlorothiazide other than smaller dosage?

DR FREIS I think that tolerance develops to chlorothiazide very slowly and to minimal or moderate degree In the patients who do develop tol erance to chlorothiazide I think that substitution of hydrochlorothiazide is helpful There doesn t seem to be any cross tolerance In addition we had one patient who had a documented rash with chlorothiazide whom we ve been able to give hydrochlorothiazide without a recurrence of the rash So it would seem to be useful also in the patients who become sensitive to chlorothiazide

DR FORD Tolerance to hydrochlorothiazide develops also These patients will respond to chlorothiazide

DR HOOBLER We have a patient who had a rash with both drugs

DR FINNERTY I would like to report three patients who showed a marked rise in the blood sugar with chlorothiazide The fasting blood sugar in creased from 150 mg per cent to 450 mg per cent with return to the control level on discontinuation of the chlorothiazide This was observed in two patients In a third patient there was no previous history of prior dia betes and three or four normal blood sugars had been obtained previously When chlorothiazide was given the fasting blood sugar increased to 290 mg per cent and returned to normal on discontinuation of the chlorothiazide I know that Dr Freis has two other patients in whom he noted a similar response

DR FREIS That was with hydrochlorothiazide

DR FINNERTY This was observed after chlorothiazide in my patients and after hydrochlorothiazide in Freis patients

DR SCHMIDT Dr Heider should patients with severe renal damage associated with hypertension have their blood pressure reduced? Will you discuss this?

DR HEIDER The effect of severe hypertension on the kidney is particularly important since this is one organ in which symptoms cannot be reversed neither can the functioning capacity be improved after a certain critical phase for each patient has been passed It is established that severe and progressive hypertension can produce renal damage particularly after it has reached the malignant phase of the disease Progressive deterioration of the kidney will occur frequently within a period of three to six months in the patient who develops malignant hypertension It is reasonable to assume that a more insidious type and degree of vascular damage will occur in the patient with less serious hypertensive vascular disease despite the fact that the hypertensive state may exist for years without producing observable renal damage

Most patients who have moderately severe to severe hypertension for a prolonged period of time will usually exhibit variable degrees of renal damage This must be considered before instituting antihypertensive therapy Effective reduction of blood pressure will usually prevent progressive anatomic damage to the kidney but the physiology of renal function is such that some reduction in glomerular filtration rate will usually accompany the initial reduction of blood pressure This is only temporary and minimal returning to control values after renal hemodynamic readjustment takes place if the blood pressure is not reduced excessively As a general rule the less the renal damage prior to induction of therapy the better the patient will tolerate blood pressure reduction For example if the glomerular filtration rate is adequate and the blood urea nitrogen is normal the blood pressure usually can be reduced to normotensive levels (130/80 to 150/100) without danger of renal decompensation However if glomerular filtration rate is severely depressed indicating marked renal damage prior to the induction of therapy even a slight reduction in glomerular filtration rate may be deleterious In such patients it is essential that the blood pressure be reduced very slowly and also a close observation should be kept on the blood urea nitrogen This is by far the most valuable laboratory aid for guiding the therapist concerning the degree of blood pressure reduction which will be tolerated by the patient with pre existent renal damage It is obvious that the greater the elevation of blood urea nitrogen the less effectively the blood pressure can be reduced When the blood urea nitrogen is above 40 repeated determinations must be made while the blood pressure is being reduced

The blood pressure should always be regulated in the upright position When there is evidence that the blood urea nitrogen is rising the blood pressure cannot be reduced any further in fact it should usually be allowed to rise slightly Thus a paradoxical renal effect exists From a functional point of view reducing the blood pressure in patients who have severely damaged kidneys may depress renal function At the same time if an adequate reduction in pressure can be achieved this will prevent progressive

renal vascular deterioration If the blood pressure is reduced excessively glomerular filtration rate and renal blood flow may remain depressed When this occurs it is readily combated by infusion of a vasopressor agent When this is done and as the blood pressure is elevated glomerular filtration rate and renal blood flow return toward the control values

Occasionally patients with nephritis may develop severe hypertension which aggravates the renal damage These patients will benefit from anti hypertensive therapy The degree of blood pressure reduction that these patients will tolerate is dependent upon the degree of renal decompensation and the same principles apply as outlined for the treatment of hypertension in patients with renal damage resulting directly from the increase in blood pressure

DR SCHMIDT Dr Heider will you comment on the treatment of patients with heart failure associated with hypertension?

DR HEIDER Patients with heart failure usually improve rather markedly with effective reduction in blood pressure particularly with the use of ganglionic blocking agents For example in one of our studies 65 per cent of the patients with heart failure showed improvement after institution of therapy with Rauwolfia and pentolinium and 81 per cent of the patients with heart failure and who received Rauwolfia and mecamylamine showed improvement Very frequently patients who have become resistant to diuretics and digitalis therapy respond adequately after effective blood pressure control is achieved with ganglionic blocking agents plus Rauwolfia

Rauwolfia alone and in combination with hydralazine exerts relatively little beneficial effect in this respect probably the patients who respond to this therapy are not as severely affected and hypertension *per se* is not of great importance in the pathogenesis of their heart failure

Since the development of chlorothiazide as an integral part in the therapy of hypertension blood pressure reduction in hypertensive patients with heart failure is indicated even more

DR SCHMIDT Dr Ford is angina pectoris associated with hypertension a contraindication to therapy?

DR FORD The combination of Rauwolfia and ganglionic blocking agents is very effective in patients with angina pectoris when the angina is secondary to the hypertension At least two-thirds or more of the patients show improvement to complete relief of this symptom

Patients with angina pectoris or coronary artery disease should not receive hydralazine without the concurrent use of Rauwolfia and chlorothiazide since this drug causes a sharp increase in cardiac output thus producing coronary insufficiency Myocardial infarction may be precipitated (Figs 1 and 2 pp 656 660) The cardiac effect of hydralazine is blocked in many patients if they are given Rauwolfia for one to two weeks before the hydralazine is started

DR SCHMIDT What do you have to say about the treatment of hypertension associated with cerebrovascular sclerosis?

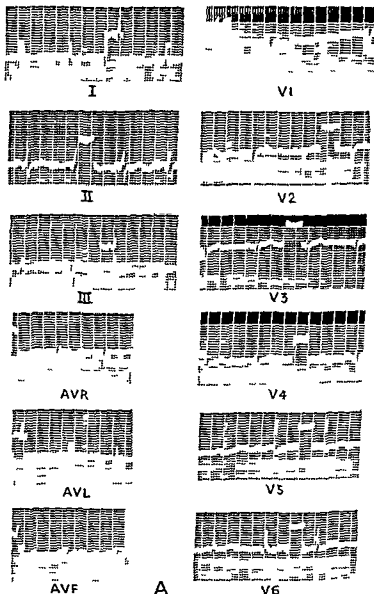


Fig 1 Electrocardiographic pattern of an acute infarction following the oral administration of hydralazine

A Electrocardiogram during the control period showing minimal evidence of coronary artery disease

Dr. Heider Cerebrovascular disease is not a contraindication to antihypertensive drugs If care is exercised in dosage in patients with cerebrovascular disease and excessive reductions of blood pressure are avoided cerebral ischemia and insufficiency do not become a problem In our experience when a cerebrovascular accident has occurred during antihypertensive therapy it has almost invariably followed a sudden rise in blood pressure due to breakthrough of the blood pressure regulation We have observed cerebral complications only following an excessive reduction in blood pressure in

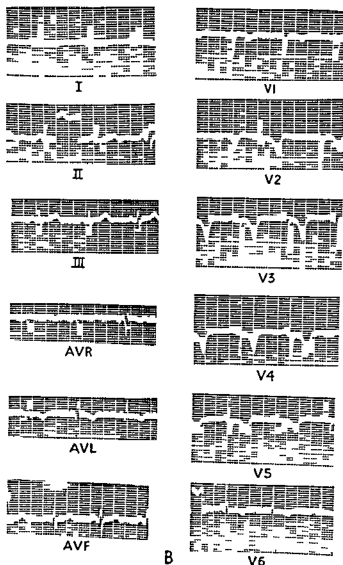


Fig 1 B Electrocardiogram taken three days after the ingestion of hydralazine which caused a severe chest pain within 30 minutes after the drug (150 mg) was taken

two patients In one of these a hemiplegia developed which was transient and cleared up within several minutes

DR SCHMIDT Dr Beem will you discuss the treatment of hypertension in the elderly patient?

DR BEEM The elderly hypertensive patient should be managed just as the younger patient is When the diastolic blood pressure is elevated, this should be treated The clinician can expect about the same response in them (Table 1 p 661) as in younger patients with hypertensive vascular disease

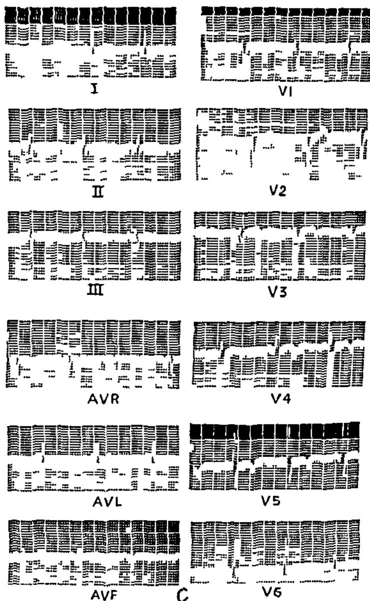


Fig 1 C Electrocardiogram taken five months later showing some resolution of the infarction pattern The residual changes confirm the diagnosis of an infarction (From A M A Arch Int Med 91 419 1953)

The problem of treatment of patients with systolic hypertension without concurrent diastolic rise is still debatable and one which I will not discuss Needless to say it is possible to reduce the blood pressure effectively in these patients with the use of milder antihypertensive agents and when this is done symptomatic improvement can often be obtained Reduction in the systolic pressure *per se* would largely be contingent on reducing cardiac output (stroke volume) which does not seem to be rational although this effect would decrease the intra arterial pressure thrust during systole and

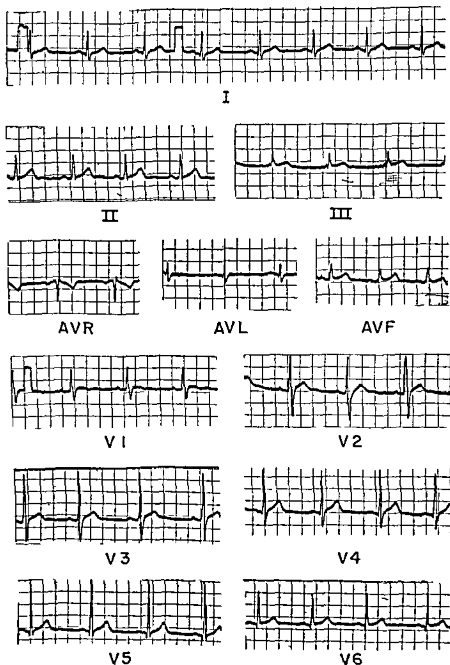


Fig 2 A Electrocardiogram during the control period in a patient with mild hypertension

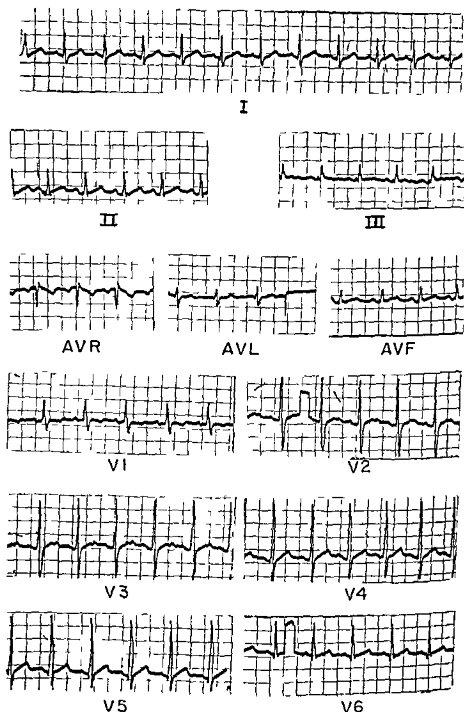


Fig 2 B Following the administration of 100 mg of hydralazine by the oral route there are alterations of the T waves similar to those seen with anoxia and myocardial ischemia or the administration of epinephrine (From A.M.A Arch Int Med *91* 419 1953)

thus reduce some of the symptomatology and possibly the incidence of ruptured peripheral vessels However if the patient has both systolic and diastolic hypertension he should be treated in the routine way (Table 1)

TABLE 1 BENEFICIAL EFFECTS OF ANTIHYPERTENSIVE THERAPY COMPARING THE ELDERLY HYPERTENSIVE (OVER 60) TO THE AVERAGE HYPERTENSIVE PATIENT

	BRADYCROTIC RESPONSE	HEADACHE	ANGINA PECTORIS	CONGESTIVE HEART FAILURE	ELECTROCARDIOGRAPHIC ABNORMALITY	RENAL DAMAGE	FUNDUSCOPIC CHANGES	X RAY CHANGE (CARDIOMEGALY)
Rauwolfia alone								
Average patient								
Number with symptoms	346	142	45	128	208	65	38	100
Per cent improved	65	70	38	16	7	0	5	—
Elderly patient								
Number with symptom	34	16	7	13	27	14	34	9
Per cent improved	38	50	29	54	15	0	0	22
Rauwolfia plus Veratrum								
Average patient								
Number with symptom	25	11	4	7	19	15	23	11
Per cent improved	44	64	75	28	66	14	—	0
Elderly patient								
Number with symptom	12	9	1	3	9	9	9	5
Per cent improved	75	78	100	0	33	17	—	-
Rauwolfia plus hydralazine								
Average patient								
Number with symptom	15	4	1	8	12	9	5	11
Per cent improved	73	50	0	13	8	11	20	0
Elderly patient								
Number with symptom	14	6	2	11	12	6	11	6
Per cent improved	43	67	0	9	8	17	9	0
Rauwolfia plus pentolinium								
Average patient								
Number with symptom	75	23	7	23	52	8	12	58
Per cent improved	67	78	71	65	40	37	59	38
Elderly patient								
Number with symptom	17	6	2	8	13	9	14	6
Per cent improved	53	67	0	38	15	0	0	50
Rauwolfia plus mecamylamine								
Average patient								
Number with symptom	80	52	10	27	67	61	17	48
Per cent improved	49	71	80	81	25	25	59	31
Elderly patient								
Number with symptom	20	14	3	8	17	11	18	9
Per cent improved	35	57	100	75	45	45	11	45

A decrease in the pulse rate of 10 beats per minute or more

Indicates total number of patients in series who were treated

— Data not available

(From Geriatrics *11* 527 1956)

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Editor's Note

The following information on treatment of older patients with hypertension is abstracted from an article by Beem and Moyer (*Geriatrics* 13 378 1958) and is inserted for information purposes Much of the original work was done by Moyer Kinard Conner and Dennis (Geriatrics *11* 527 1956)

RESULTS OF TREATMENT COMPARING THE AVERAGE HYPERTENSIVE PATIENT WITH HYPERTENSIVE PATIENTS ABOVE THE AGE OF 60

A study of 443 patients was undertaken to determine the relative efficacy and safety of antihypertensive therapy in elderly patients This series included 346 patients under and 97 patients above the age of 60 years Both age groups had a considerable and similar incidence of congestive heart failure angina pectoris previous cerebrovascular accidents and funduscopic changes associated with hypertension and arteriosclerosis However there was a larger percentage of elderly patients with renal disease and electrocardiographic abnormalities The two groups were compared and contrasted

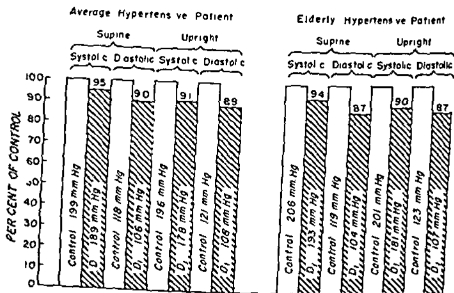


Fig 3 Blood pressure response to Rauwolfia alone comparing the response of the average patient with the response of the elderly hypertensive above the age of 60 The over all blood pressure responses were similar (From Geriatrics *11* 527 1956)

in terms of the blood pressure reduction achieved improvement in other clinical manifestations of the disease and incidence and severity of adverse reactions

Results of Treatment. The mean arterial blood pressure reduction was virtually the same in both age groups A reduction of 20 mm Hg or more was obtained in 41 per cent of the elderly groups by treatment with Rauwolfia alone and in 90 per cent of those patients treated with Rauwolfia and mecamylamine From one fourth to one half of these patients became normotensive as defined by a blood pressure less than 150/100 mm Hg The over all effect on blood pressure was approximately the same (Figs 3 to 6)

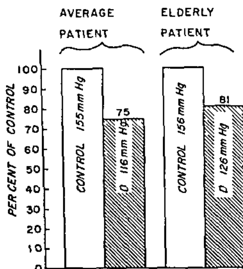


Fig 4 Mean blood pressure response to Rauwolfia given in combination with hydralazine comparing the average patient with hypertension with the elderly patient with hypertension The response is expressed in per cent of control value The response was similar (From Geriatrics *13* 378 1958)

The improvement of hypertensive signs and symptoms in the two groups was quite similar From one third to one half of the patients benefited by improvement in headache angina pectoris congestive heart failure reduction in pulse rate and cardiac enlargement and by a sense of well being Improvement was infrequently observed in the eyegrounds renal function or in the electrocardiogram in older patients perhaps as a result of more advanced arteriosclerosis

The side effects attributed to drug therapy were similar at all ages and

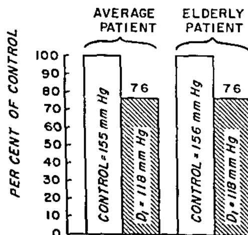


Fig 5 Mean blood pressure response to pentolinium (Ansolysen) given in combination with Rauwolfia comparing the elderly with the average hypertensive patient The over-all blood pressure response was similar (From Geriatrics 13 378 1958)

antihypertensive therapy proved essentially as safe in these patients above 60 years of age as in the younger age group

It has required several years of careful study to determine the effect of antihypertensive drug therapy upon the prognosis of this variable and chronic syndrome Without such treatment renal function as determined by glomerular filtration rate and renal blood flow progressively declined and the incidence of complications increased as blood pressure rose regardless of age Effective reduction of blood pressure by these drugs appeared to decelerate the renal vascular deterioration in patients with moderately severe severe and accelerated stages of hypertension It is reasonable to expect a similar beneficial influence upon other vascular beds thereby conserving function in vital organs

Treatment Recommendations The preceding observations suggest that antihypertensive therapy may be considered regardless of age in certain

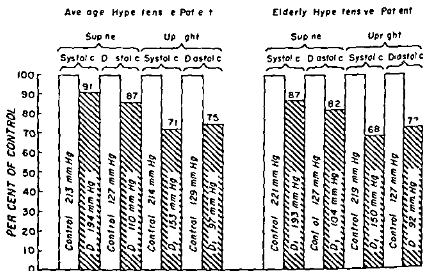


Fig 6 Blood pressure response to mecamylamine (Inversine) given in combination with Rauwolfia The response in the elderly patients was similar to that observed in the average hypertensive patients (From Geriatrics *11* 527 1956)

patients selected on the basis of considerable and sustained diastolic hypertension and evidence of progressive vascular deterioration However certain principles are essential if optimal therapeutic results are to be achieved and dangerous reactions to be avoided Large individual differences exist in blood pressure reactivity and tolerance to side effects with most available drugs Consequently an appropriate regimen must be designed for each patient All effective antihypertensive agents have certain potentially adverse effects which must be guarded against or promptly and actively corrected as will be discussed later

Therapy is initiated with the less potent drugs and if the response is suboptimal within the tolerable dosage range other agents are added to the regimen Since each of these drugs has a different dosage requirement and duration of effect each must be carefully and individually applied The more potent compounds are given in small doses and the amount and

frequency of administration gradually increased until the desired effect is achieved This process referred to as titration requires regular and frequent observation of the blood pressure and other signs and symptoms To achieve maximum benefits periodic readjustment of dosage is necessary because of multiple influences upon blood pressure regulation such as changes in fluid and electrolyte balance including diurnal or seasonal variations environ mental stress and the development of drug tolerance The objective is to reduce elevated blood pressure and its consequences as effectively as pos sible short of intolerable side effects or compromised vital circulation par ticularly in severe or accelerated hypertension

Table 2 outlines our therapeutic program for the elderly patient with hypertension The elevated systolic pressure frequently observed in older patients with arteriosclerosis is distinguished from and not treated as diastolic hypertension

TABLE 2 THERAPEUTIC APPROACH TO THE ELDERLY PATIENT WITH HYPERTENSION

SEVERITY OF HYPERTENSION	INITIAL THERAPY	ADJUNCTIVE THERAPY
Systolic blood pressure elevation diastolic blood pressure <100 mm Hg	None	None
Diastolic blood pressure >100 mm Hg but <120 mm Hg	Chlorothiazide† or Hydrochlorothiazide†	Rauwolfia or Rauwolfia + hydralazine
Diastolic blood pressure >120 mm Hg	Chlorothiazide† and Rauwolfia or Hydrochlorothiazide† and Rauwolfia	Hydralazine or ganglion blocking agent
Severe progressive hypertension	Chlorothiazide† and Rauwolfia or Hydrochlorothiazide† and Rauwolfia	Ganglion blocking agent‡

Adjunctive therapeutic agent to be added to regimen if initial therapeutic agent i found to be inadequate alone
† Chlorothiazide 500 mg b i d. or hydrochlorothiazide 50 mg b i d
‡ Must be added without delay when indicated

Ordinarily we do not use potent antihypertensive drugs in patients with severe nitrogen retention (blood urea nitrogen above 60 mg per cent) fol lowing a recent myocardial infarction or following a recent cerebrovascular accident unless it becomes urgent that extremely elevated blood pressure be cautiously reduced

Chlorothiazide Because of the many implications of the pathogenic role of fluid and electrolyte balance in hypertension we have long sought an effective and safe means of enhancing the excretion of sodium chloride and water With the synthesis of chlorothiazide and the demonstration of saluretic and diuretic properties in laboratory animals and man studies were initiated with this compound in hypertension

Chlorothiazide when given alone is mildly antihypertensive in some patients Chlorothiazide markedly augments the blood pressure reduction by other agents It increases the excretion of sodium chloride and water and

obviates the need for a rigidly restricted sodium diet in many patients This is particularly valuable in elderly patients who tend to eat poorly and who find a low salt diet most unpalatable The drug has been well tolerated and a relatively standardized dosage is frequently possible without the complex titration procedures required by rigorous hypotensive agents

These attributes have led us to consider chlorothiazide as basal therapy and we now administer it as the initial drug in previously untreated patients Unless severe and rapidly progressive hypertension is present it is first given alone in a dose of 0 5 gm twice daily Hydrochlorothiazide in a dose of 50 mg given twice a day is equally effective The onset of antihyper tensive action may be observed within 12 to 72 hours and the maximum effect is usually obtained within three to 14 days The duration of this blood pressure response as judged upon withdrawal of therapy is one to four days Early or significant tolerance is rarely a problem upon continued administration for as long as several months

Some patients with mild degrees of hypertension have been controlled by chlorothiazide in combination with moderate restriction of dietary so dium In the others after an interval of a few days to a few weeks we add Rauwolfia and sometimes other drugs as discussed later Chlorothiazide and Rauwolfia prepare the patient for other agents by minimizing the dosage and side effects of the latter Stepwise addition of such drugs when necessary usually results in optimal blood pressure control Although mildly antihypertensive when given alone chlorothiazide is even more impressive in its augmentation of vasodepressor drugs such as Rauwolfia Veratrum hydralazine and ganglion blocking agents Certain patients resistant to previously available drugs have responded well to the addition of chloro thiazide When adding chlorothiazide to another previously initiated drug regimen it is very important to avoid excessive blood pressure reduction Since patients treated with ganglion blockade or sympathectomy appear to be much more highly responsive initial dosage of chlorothiazide should be 0 125 to 0 25 gm once or twice daily Thereafter this dose may be cau tiously increased by increments of 0 125 to 0 25 gm at intervals of three to seven days if necessary

When adding chlorothiazide to ganglion blockade therapy (even though an inadequate response may have resulted from the latter) it appears essen tial to reduce the dose of the ganglion blocking agent by approximately one half initially thereafter observing the patient very closely until retitra tion and final dosage adjustment result in stable control of blood pressure Although the antihypertensive effect of chlorothiazide is nonpostural gan glion blockade or sympathectomy produces an orthostatic effect of course which must be carefully controlled as will be outlined later We have found it possible to treat most patients with smaller doses of the previously avail able hypotensive drugs It has rarely been necessary to exceed a daily maxi mum of 0 25 mg of reserpine 100 mg of Rauwolfia root 300 mg of hydralazine or 15 to 20 mg of mecamylamine

Since chlorothiazide is saluretic and diuretic as well as antihypertensive in action it is particularly applicable in those hypertensive cases compli cated by congestive heart failure or fluid and electrolyte retention accom panying other disorders The very notable resistance to previous antihyper tensive agents in the presence of edema which is particularly common in older patients is readily reversed by diuresis

Although chlorothiazide is relatively well tolerated a small percentage of

patients experience anorexia nausea or more rarely vomiting These gastro intestinal effects usually subside rapidly but may require reduction of the dose or temporary discontinuation of the drug for 24 to 48 hours Infre quently skin rash may occur but it appears to clear within a few days after discontinuation of therapy Muscle cramps and slight paresthesias some times result but they are rarely troublesome if dosage and administration are properly adjusted

Although chlorothiazide characteristically increases the excretion of sodium and chloride most markedly there is also some kaluretic action which in certain patients may result in depression of serum potassium levels In our patients this has not been a serious problem however it appears desirable to observe patients for evidence of hypokalemia and when indicated to reduce the dosage or frequency of administration of chloro thiazide and/or replace the body stores of potassium by liberal intake of orange juice or by other means We carefully endeavor to avoid digitalis intoxication which of course may be precipitated by hypokalemia

Although it is possible that hyponatremia hypochloremia and alkalosis may be precipitated by the saluretic action of chlorothiazide our patients have rarely been so troubled Perhaps this is because we usually avoid marked restriction of salt intake and we apply great caution in the use of the drugs in patients with salt losing disorders of any type

Rauwolfia If the response to chlorothiazide alone is not optimal within a few days to a few weeks depending on the urgency of the individual condition we then add 200 mg of Rauwolfia whole root (or 8 mg alseroxy lon or 0 5 mg reserpine) daily for two weeks thereafter reducing the dose by approximately 50 per cent It seems undesirable to use larger amounts of Rauwolfia inasmuch as efficacy is not sufficiently enhanced to compen sate for the increased side effects There is little difference in blood pressure reducing activity between these forms of Rauwolfia when used in appro priate dosage

Orally administered, Rauwolfia exerts a mild antihypertensive action which may require several weeks before maximum effect is obtained Simi larly its duration of action is quite prolonged and the effect may be manifest for several weeks after discontinuation of therapy Tolerance to the blood pressure reducing effect has not presented a problem Rauwolfia decreases the pulse rate and many patients experience a sense of well being and considerable symptomatic improvement Headache congestive failure and cardiac dilatation may be improved Angina pectoris is sometimes dimin ished particularly if there has been a pre existing tachycardia

Rauwolfia side effects rarely have been serious when the drug has been administered orally and in the dosage recommended Blood pressure reduc tion characteristically is not excessive and the drug is usually safe in patients with cardiac renal or cerebrovascular disease Nasal stuffiness occurs fre quently although it tends to diminish somewhat in intensity as treatment is continued This symptom sometimes requires the administration of nasal vasoconstrictor substances Many patients experience more frequent bowel movements from stimulation of gastrointestinal motility Appetite is often increased and some weight gain may result Nausea blurred vision edema dizziness unsteady gait Parkinson like syndrome weakness lethargy night mares and aggravation or precipitation of peptic ulceration occasionally occur The most serious though relatively infrequent effect has been depres sion often with agitation which may culminate in suicide This is more apt

to occur after prolonged administration of the drug and often may be preceded by a change in sleep pattern agitation or early morning insomnia It requires immediate withdrawal of the drug psychiatric care and precautions against suicide The incidence of this complication appears to be greater following the administration of reserpine than after the administration of the alseroxylon fraction (Rauwiloid)

Hydralazine Some patients inadequately responsive to chlorothiazide and Rauwolfia benefit from the addition of hydralazine to the treatment regimen Pretreatment with the former drugs is valuable because it serves to minimize side effects and to enhance the efficacy of hydralazine

Hydralazine is added in an initial dose of 10 mg four times daily After one week the dose may be increased to 25 mg four times daily By the titration process each dose is increased 25 mg usually at weekly intervals until the blood pressure is adequately reduced or side effects become excessive In most patients we arbitrarily limit the dose to a maximum of 400 mg a day hoping to avoid serious toxicity

Headache tachycardia palpitation anginal pain and exertional dyspnea are not infrequently produced by hydralazine Less often nausea vomiting fever dizziness paresthesias nasal congestion rash and edema may occur Angina pectoris or other evidence of serious coronary artery disease congestive failure and cerebrovascular insufficiency are reasons for caution Pretreatment with Rauwolfia is recommended in an effort to block the cardiac stimulation which has been attributed to hydralazine In a few patients a lupus erythematosus like reaction may occur particularly when large doses have been administered over a prolonged period of time Arthropathy skin eruption fever and a positive L E cell phenomenon may occur These or related signs and symptoms indicate the need for immediate withdrawal of the drug Occasionally it is necessary to administer adrenocortical steroids in an effort to reverse the process In an attempt to prevent this serious toxicity it is desirable to limit the dosage as previously suggested

Ganglion Blocking Drugs These compounds including hexamethonium pentolinium (Ansolysen) chlorisondamine (Ecolid) and mecamylamine (Inversine) are potent vasodepressors and considerable care is required to avoid excessive blood pressure reduction and to minimize side effects Their application is usually restricted to patients with the more severe grades of hypertension inadequately controlled by the drugs previously discussed Pretreatment with chlorothiazide and Rauwolfia reduces the dosage requirement augments blood pressure response and moderates certain of the side effects of ganglion blocking agents Although such basal therapy is advantageous unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension

Treatment may be initiated with the oral administration of 2 5 mg of mecamylamine 20 mg of pentolinium or 25 mg of chlorisondamine twice daily Individual titration of dosage is essential (Fig 7) and may be accomplished by increasing the amount or frequency of administration to a point of optimal blood pressure response or until limited by side effects Since the antihypertensive action of ganglion blockade is orthostatic the titration procedure should be guided by the blood pressure recorded in the upright position Blood pressure may be recorded frequently at home or the 30 second standing rest of Smirk may be used to elicit orthostatic symptoms Advantage of the postural effect on blood pressure may be taken by elevating the head of the bed six to eight inches if necessary to maintain lower

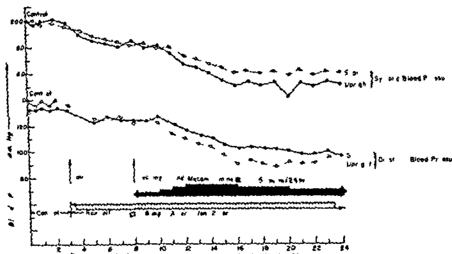


Fig 7 Blood pressure response to a combination of mecamylamine and Rauwolfia showing the dose titration of the ganglionic blocking agent (mecamylamine) The Rauwolfia was given first This was followed by the administration of mecamylamine The initial dose of the mecamylamine was small and inadequate but this was increased weekly in small increments until the desired reduction in blood pressure was obtained As the blood pressure was controlled for a prolonged period the dose requirement of the blocking agent decreased

arterial pressures nocturnally Periodic readjustment of dosage is essential because of the changes in reactivity which occur in the patient from time to time Also adjustment of the dosage schedule for periods of recurring stress during the day improves the blood pressure regulation (Fig 8) Edema

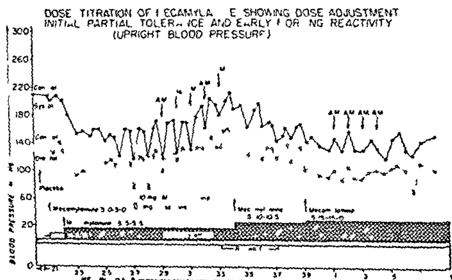


Fig 8 Dose titration of mecamylamine showing dose adjustment and early morning reactivity *In* patients receiving ganglionic blocking agents who experience excessive reduction of blood pressure at certain times during the day adjustment of the dosage schedule is necessary until the blood pressure remains more or less constant throughout the day (*From A M A Arch Int Med 98 187 1956*)

and various forms of stress often decrease responsiveness to ganglion blocking agents Depletion of body stores of fluid and electrolytes may greatly intensify the blood pressure reduction The addition of chlorothiazide augments the blood pressure response in patients who are already receiving effective doses of ganglion blocking agents and it is usually necessary to reduce the dose of the latter by one half or more when this is done

Excessive blood pressure reduction must be carefully avoided especially in the presence of severe renal disease and impaired coronary or cerebral circulation Regrettably some patients do not present themselves for treatment prior to the progression of renal vascular deterioration with marked nitrogen retention In these patients a reduction of blood pressure may decrease further the renal blood flow and glomerular filtration rate and may increase nitrogen retention Therefore vigorous antihypertensive therapy may be contraindicated or may have to be terminated if further impairment of renal function occurs Although sharp reduction of blood pressure represents a potential factor in the production of cerebral ischemia and orthostatic dizziness or faintness occur frequently most cerebrovascular accidents during antihypertensive therapy are associated with a sudden rise in blood pressure rather than with hypotension The recumbent posture may be used to combat excessive blood pressure fall Pressor amines may be administered if necessary but ganglion blocked patients may respond excessively therefore small doses and great caution are required

The patient must be regularly and frequently observed to avoid or promptly correct troublesome or dangerous side effects It is essential to forewarn him and outline the manner of reporting and handling each adverse effect by dosage adjustment or counteracting measures

Dryness of the mouth impaired visual accommodation photophobia gastrointestinal atony impotence difficult micturition increased sensitivity to cold and susceptibility to heat may occur On occasion the use of hexamethonium has been associated with interstitial pneumonitis and mecamylamine with a coarse tremor and psychosis which are more apt to occur in the presence of uremia severe cerebrovascular disease and excessive dosage Dryness of the mouth may require pilocarpine nitrate 2 5 to 5 mg orally one to four times daily Visual accommodation may be improved by reading glasses or pilocarpine Dark glasses are useful when photophobia is present Gastrointestinal atony first manifests itself as constipation which may occur promptly on the initiation of therapy Indeed it may be most severe during the early stage of therapy It is essential that it be vigorously treated from the outset by laxatives such as 30 cc of milk of magnesia or 10 to 15 cc of Cascara sagrada alone or in combination if necessary Neostigmine 15 to 30 mg or bethanechol chloride 5 to 20 mg orally before each meal may be required in some patients in others however they may cause severe abdominal cramps Trial and error are necessary in determining the best manner of handling this problem in each patient Unless constipation is promptly corrected and a daily bowel movement maintained paralytic ileus may result If this occurs the patient must be hospitalized immediately and neostigmine given 1 mg intramuscularly every hour until a bowel movement occurs and ileus is relieved

Although ganglion blocking agents require great care in their application they are valuable in controlling severe and malignant hypertension Their efficacy is enhanced and their adverse reactions moderated by basal therapy with chlorothiazide and Rauwolfia

CONCLUSIONS

A comparative study of antihypertensive therapy in patients above and below 60 years of age has indicated that treatment carefully applied in selected patients may be about equally well tolerated in both age groups Similar blood pressure reduction and improvement in signs and symptoms of hypertensive cardiovascular disease may be obtained in both age groups It appears that such therapy may be indicated in certain elderly patients with severe and sustained diastolic hypertension troublesome symptoms related thereto and evidence of progressive vascular deterioration Basal treatment with chlorothiazide and the stepwise addition of Rauwolfia hydralazine or a ganglion blocking drug where indicated constitute an effective antihypertensive regimen applicable to all age groups

Part V

A THE SURGICAL APPROACH TO ESSENTIAL HYPERTENSION

B THE EFFECT OF THERAPY ON PROGNOSIS IN PATIENTS WITH HYPERTENSION

C SUMMARY TODAYS RECOMMENDATIONS FOR DRUG THERAPY OF HYPERTENSION

A THE SURGICAL APPROACH TO ESSENTIAL HYPERTENSION

Physiologic-Surgical Consideration in Hypertension

ROBERT BOWER
Hahnemann Medical College and Hospital

The surgical treatment of hypertension was initiated in this country in 1925 when Rowntree and Adson[1] reported a hypertensive patient for whom bilateral lumbar sympathectomy was done It was immediately evident that this was an inadequate operation and during the succeeding 20 years increasingly radical interruptions and excisions of the sympathetic nerves were performed in an effort to control the progressive forms of hypertensive disease The subdiaphragmatic splanchnicectomy reported by Adson the supradiaphragmatic splanchnicectomy reported by Peet[3] the thoracolumbar splanchnicectomy and sympathectomy reported by Smithwick[4] and finally the "total" sympathectomy reported by Grimson appeared in this chronologic order Historically surgical procedures on the adrenal gland consisting of either denervation or partial removal were employed in the treatment of hypertension after interest in sympathectomy appeared DeCourcey and DeCourcey[6] found that 75 to 80 per cent removal of adrenal tissue was necessary to produce definite alteration in the hypertensive pattern Zintel *et al*[7] and Bowers[8] reported on groups of patients for whom subtotal adrenalectomy alone or in addition to sympathectomy was performed for hypertension Thorn *et al*[9] and Blakemore *et al*[10] reported the results in groups of hypertensive patients in whom total adrenalectomy was performed alone or in combination with sympathectomy The physiologic aspects of sympathectomy and adrenalectomy will be discussed separately

SYMPATHECTOMY

For the purposes of discussion the physiologic considerations in sympathectomy may be subdivided as follows (1) lowering of basal blood pressure (2) abolition of sudden elevations in blood pressure (3) alterations in renal blood flow and function and (4) production of norepinephrine in sympathetic tissue Side effects (without further discussion) are the following increased vasoconstriction and sweating in arms postural hypotension increased motility of colon failure of ejaculation in the male impaired perception of pain arising in abdominal viscera

Lowering of Basal Blood Pressure Approximately two thirds of patients subjected to sympathectomy will have postoperative decrease in basal blood pressure

The mechanism of this decrease is by adequate removal of sympathetic vasomotor tone to a large segment of the total body vascular bed including kidneys abdominal viscera and lower extremities Undoubtedly decrease in peripheral resistance as a result of this denervation is a major factor in the hypotensive response Of importance in addition to diminished peripheral resistance however is an increase in the capacity of the vascular bed in the denervated area especially in the postarteriolar vessels with a resulting vascular reservoir and secondary decrease in cardiac output

Abolition of Pressor Response An abnormal pressor response to a variety of stimuli is characteristic of the hypertensive patient In the sympathectomized patient the removal of vasoconstrictor power in the denervated area is probably the most potent factor in the abolition of this hypertensive response An additional factor is modification of the release of pressor substances from the adrenal medulla by adrenal denervation The release of epinephrine and norepinephrine from the adrenal medulla appears to be entirely under neurogenic control Stimulation of the splanchnic nerves results in liberation of the epinephrines from the adrenal glands as does hypothalamic stimulation by a variety of stressful situations and also the administration of such drugs as strychnine nicotine and morphine The observed increases in epinephrine output are eliminated by denervation of the adrenals [11]

It would be expected therefore that interruption of the sympathetic nerves to the adrenal glands by splanchnicectomy would enhance the effect of peripheral and splanchnic denervation in diminishing the magnitude and the frequency of sudden rises in blood pressure under stress in hypertensive patients That such is indeed the case was demonstrated by Wilkins and Smithwick[12] in preoperative and postoperative studies in hypertensive patients subjected to bilateral thoracolumbar sympathectomy Follow up studies showed that stimuli which preoperatively caused widespread vasoconstriction and marked increases in blood pressure postoperatively caused little or no response It was also noted that this effect was of long duration and was independent of alterations in the basal pressure

Renal Blood Flow and Function It has repeatedly been shown since Claude Bernard s discovery of the renal vasomotor nerves (1895) that direct or reflex stimulation of the renal sympathetic fibers produces marked diminution in renal blood flow Such transient reduction in renal blood flow in response to appropriate stimuli can be demonstrated in normal[13] and in hypertensive[14] subjects As Smith emphasizes however it has not been demonstrated that permanent or sustained diminution in renal blood flow results from chronic stimulation of the renal sympathetic nerves nor that decreases in renal blood flow observed in hypertensive patients are attributable to neurogenic impulses arriving in the kidneys via the splanchnic sympathetics It is not surprising therefore that clinical studies of renal blood flow and renal function in hypertensive individuals following sympathectomy alone or in combination with adrenalectomy have not consistently shown improvement

Page[15] found no alteration in renal function in two patients following unilateral and bilateral renal denervation respectively

DeTakats[16] states that sympathectomy has not in his experience with hypertensive patients been followed by demonstrable improvement in renal function

Peet[17] reported that of 55 patients showing impaired renal function before operation 37 per cent showed improved function and 52 per cent showed no change five to 11 years after sympathectomy for hypertension

Barker *et al* [18] studied renal function in a small group of patients before and after sympathectomy and subtotal adrenalectomy Renal plasma flow was increased postoperatively in three of the five patients studied For many years the concept was held that the elevated blood pressure in patients *with hypertensive disease was essential for maintenance of renal function* and that therapeutic reduction in pressure would have a detrimental effect on the kidney This misconception was laid to rest almost 25 years ago by the work of Page[19] and others who demonstrated that blood pressure reduction in the hypertensive patient did not result in deterioration of renal function

Talbot and Smithwick [0] correlated severity of renal vascular disease as determined by renal biopsy with alterations in GFR and RBF in hypertensive patients before and after bilateral thoracolumbar sympathectomy It was found that alterations in renal hemodynamics accurately reflected the degree of vascular pathology It was also shown by follow up studies that except for transient decrease in GFR in the postoperative period both GFR and RBF were maintained at preoperative levels for long periods of time in these postsympathectomy patients

The medical counterpart to this has been supplied recently by Moyer *et al* [1] in their studies on the renal vascular status of hypertensive patients It was shown that decreases in glomerular filtration rate and renal blood flow in hypertensive patients were related to the duration of the disease and to the magnitude of the blood pressure elevation In addition follow up studies showed, as was the case with sympathectomy that renal vascular deterioration could be arrested for long periods by adequate therapeutic reduction in blood pressure and that conversely in untreated patients renal vascular deterioration was progressive ending eventually in renal failure Of special interest is a small group of patients reported by Moyer who had onset of hypertension rapidly associated with unilateral renal arterial occlusion These patients all manifested marked diminution in GFR and RBF in the opposite uninvolved kidney Reduction in blood pressure either by surgery or by drug therapy in these patients with hypertension of short duration resulted in marked improvement in both GFR and RBF in the uninvolved kidney

These observations suggest that irreversible changes in renal hemodynamics occur as hypertensive disease progresses into the more advanced stages and that although reduction in blood pressure by surgical or medical management will not usually restore existing loss it will arrest the progression of renal vascular disease There is also the probability that early impairment of renal function or impairment associated with hypertension of acute onset and short duration can be reversed toward normal by adequate reduction in blood pressure

Production of Norepinephrine in Sympathetic Tissue Two observations in hypertensive patients subjected to sympathectomy raise the question of a possible humoral effect originating in extra adrenal sympathetic nervous

tissue specifically the ganglionated sympathetic chains The first of these observations is a clinical one and involves variations in magnitude and duration of the hypotensive effect of sympathectomies of different extent Thus the subdiaphragmatic splanchnicectomy of Adson the lumbodorsal sympathectomy of Smithwick and the total sympathectomy of Grimson represent in terms of quantity of sympathetic tissue excised three distinct degrees of removal the adrenal glands being denervated in all three The more radical the extirpation of sympathetic tissue in general the greater the hypotensive effect and probably the more lasting To say that this simple observation indicates an important humoral function of sympathetic nerve tissue would be to ignore the obvious relationship between the amount of sympathetic tissue removed and the extent of the vascular bed which is deprived of its vasomotor innervation A second set of observations however experimental in character point more specifically to a humoral factor derived from sympathetic nerve tissue Cannon[2] and his colleagues in their classic work on the autonomic nervous system identified a substance in adrenalectomized animals resembling epinephrine in its action which apparently was released directly from sympathetic nerve tissue This substance which they named sympathin has since been demonstrated to be norepinephrine

More recently Raab and Lepeschkin[23] studied the relationship between blood pressure levels electrocardiographic changes and the effects on the heart of sympathomimetic amines of the norepinephrine group released from functioning sympathetic tissue The following pertinent observations were made

1 Electrocardiographic abnormalities identical to those seen in hypertensive heart disease can be produced experimentally by administration of sympathomimetic amines apart from any consistent hypertensive effect

2 The heart muscle of many hypertensive individuals contains abnormally large amounts of chromogenic catechol amines

3 The concentration of catechol amines in the myocardium of sympathectomized animals is greatly reduced

These observations are interpreted as suggesting an important role for endogenous sympathomimetic amines in the production of electrocardiographic and functional abnormalities of the heart by direct chemical action in hypertensive individuals They further suggest that the beneficial effect of sympathectomy in some hypertensive individuals may be in part due to depression of production of norepinephrine in the adrenal medulla and in sympathetic ganglia Such an hypothesis would offer a partial explanation for the improvement after sympathectomy of some hypertensive patients in whom lowering of the basal blood pressure is not attained

PHYSIOLOGIC BASIS FOR ADRENAL SURGERY IN HYPERTENSION

The presence of hypotension in addisonian patients and the frequent occurrence of hypertension in patients with hyperplasia or neoplasms of the adrenal cortex caused investigators to speculate on the role of the adrenal gland in hypertensive states long before total adrenalectomy became a practical possibility Goldblatt [4] and Page-[5] noted independently that experimental hypertension could not be fully maintained in the presence of

inadequately treated adrenal failure Page and Lewis [6] subsequently showed after adrenal steroids appeared that such hypertension could be maintained if adequate substitution therapy were given With the appearance of ACTH and cortisone it was found clinically that administration of these compounds to patients with pre existing hypertension often produced an exacerbation of the disease Finally in the last decade it has been demonstrated that surgical ablation of adrenal cortical function frequently has a sustained hypotensive effect on patients with severe progressive hypertensive disease [7,8,9]

Neither the part that the adrenal cortex plays in the maintenance of blood pressure at normal levels nor its role in essential hypertension is completely understood The commonly accepted concepts of action at the moment include (1) changes in excretion and in concentration at the cellular level of sodium and potassium (2) sensitization by the steroids of arterioles to the effects of circulating pressor substances and (3) a permissive role in making possible the formation of circulating pressor substances

Electrolyte Effects Experimentally Bohr *et al* [7] found that lowering the ratio of intracellular to extracellular potassium in vascular smooth muscle results in increased contractibility Since it is known that DCA is hypertensive in action and since DCA produces sodium retention and interferes with entrance of potassium into cells it is suggested that lowering of the K_i K_o ratio by reduction in cellular potassium may be a mode of action of the adrenal cortex Clinically Thorn *et al* [9] found an increased capacity to excrete sodium to be the outstanding physiologic result of bilateral complete adrenalectomy in a group of severe hypertensive patients Sodium diuresis always preceded significant drops in the basal blood pressure but not every patient who lost sodium demonstrated a corresponding reduction in pressure

Vascular Reactivity Perera [8] and Bohr [7] have emphasized that DCA potentiates the contractile response of vascular smooth muscle to epinephrine As mentioned previously Bohr suggested that this may reflect changes in potassium concentration at the cellular level Conversely Salmoiraghi and McCubbin [9] found that vascular reactivity was depressed in adrenalectomized dogs

Formation of Pressor Substances Lewis and Goldblatt[10] demonstrated that renin substrate formation is deficient in adrenal cortical failure Helmer and Griffith[11] observed that DCA stimulates the formation of renin substrate in the rat

The experimental and clinical data suggest that the adrenal cortex has multiple influences in the genesis and maintenance of hypertension not only of adrenal origin but also in essential and renal hypertension It is further apparent that the objective of the surgeon when operating for hypertension is to produce a state of borderline adrenal insufficiency Since it is most difficult to gauge the functional potential of a given quantity of adrenal tissue which may be left behind and since a satisfactory level of function can be attained with substitution therapy complete bilateral adrenalectomy is desirable

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SUMMARY OF EXPERIENCE WITH SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

Figure 1 summarizes my experience with splanchnicectomy for essential hypertension from October 1 1938 through December 31 1957 During this period a total of 2708 cases were operated upon an average of 135 per year The largest number in any one year was 358 in 1947 It is interesting to consider this experience by dividing it into two periods 1938 through 1947 and 1948 through 1957 In the first period other therapeutic agents or measures generally available were sedatives weight reduction psychotherapy low sodium diets rice diet thiocyanate and nitrates These singly or collectively did not seem to be sufficiently effective in the control of hyper

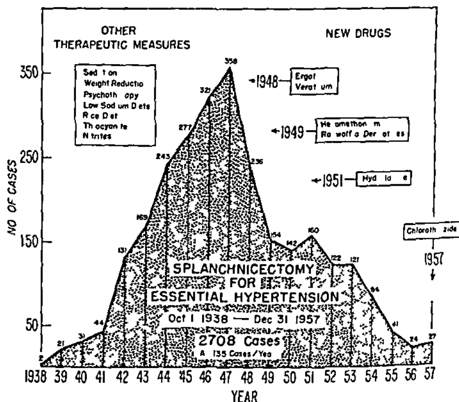


Fig 1

tensive cardiovascular disease in the hands of most physicians The number of cases operated upon during these years rose precipitously Starting with 1948 and continuing through 1955 there was almost as precipitous a fall in the number of cases operated upon each year This would seem to be related to the introduction of the newer hypotensive drugs commencing with the ergots and Veratrum and hexamethonium Rauwolfia compounds hydralazine and chlorothiazide following in that order During the past two years we have operated upon an average of 25 patients per year The number of operations being performed seems to be increasing at the present time and I expect that there will be a further modest increase in this figure because splanchnicectomy does have real value in the management of refractory cases and in the long term management of the disorder in young patients

EFFECT OF SPLANCHNICECTOMY UPON BLOOD PRESSURES CARDIOVASCULAR DISEASE AND SYMPTOMS

Table 1 summarizes the effect of splanchnicectomy upon blood pressure cardiovascular disease and symptoms An attempt has been made to bring out the influence of the duration of follow ups upon these three aspects of the problem Patients whom we have personally checked at various time intervals after operation serve as the basis for the evaluation of the effect of operation It would appear that the percentage of patients who are improved or who show no change or who are worse in these three respects remains *relatively constant up to 10 years* Patients checked in the 10 to 19 year follow up period show more evidence of cardiovascular deterioration and an increase in symptoms

It seems proper to emphasize that patients followed 10 to 19 years had little opportunity to benefit from supplementary treatment with the newer hypotensive agents Even so there is good evidence that splanchnicectomy

TABLE 1 EFFECT OF SPLANCHNICECTOMY UPON BLOOD PRESSURE CARDIOVASCULAR DISEASE AND SYMPTOMS

1116 Cases Followed 1 to 4 Years
530 Cases Followed 5 to 9 Years
234 Cases Followed 10 to 19 Years

	TIME FOLLOWED	IMPROVED	NO CHANGE	WORSE
Blood pressure	1– 4 Years	48%	40%	12%
	5– 9 Years	41%	45%	14%
	10–19 Years	50%	34%	16%
Cardiovascular disease	1– 4 Years	33%	60%	7%
	5– 9 Years	36%	57%	7%
	10–19 Years	42%	21%	37%
Symptoms	1– 4 Years	74%	24%	2%
	5– 9 Years	76%	19%	5%
	10–19 Years	70%	5%	25%

is of value in reversing cardiovascular changes and holding them in check for long periods of time It is also probable that with the aid of relatively small doses of hypotensive agents the results in the future will be considerably better

EFFECT OF SPLANCHNICECTOMY UPON ELEVATIONS OF BLOOD PRESSURE DUE TO REFLEX VASOCONSTRICTION

A number of years ago Wilkins and Culbertson[1] carried out certain observations before and after splanchnicectomy in the course of studying some of the physiologic effects of this operation They found that sudden elevations of blood pressure due to reflex vasoconstriction were greatly minimized or abolished This could be well demonstrated by the response to the Valsalva maneuver before and after operation When the patient exhales against positive pressure the blood pressure falls sharply thus initiating widespread vasoconstriction in an attempt to elevate it again Before operation this resulted in sharp rises in blood pressure which often reached levels far above those noted prior to stimulation After operation these sharp rises were greatly minimized or abolished To me these findings

TABLE 2 COMPARISON OF MEDICAL AND SURGICAL CASES FOR TEN YEAR DEATH RATES BY SEX AND GROUP

			MEDICAL (No Operation)			SURGICAL (Splanchnicectomy)				
		Total cases	Known dead	%	Total cases	Known dead	%	Chi square	P	Sig
Males Group	I	47	18	38	106	21	20	4 93	< 05	S
	II	151	94	62	459	180	39	23 45	< 001	H S
	III	101	90	89	169	94	56	31 14	< 001	H S
	IV	79	79	100	95	70	74	22 19	< 001	H S
Females Group	I	41	7	17	139	13	9	1 21	< 2	N S
	II	142	53	37	618	130	21	15 88	< 001	H S
	III	48	28	58	175	65	37	6 12	< 05	S
	IV	40	36	90	62	44	71	4 14	< 05	S

seem important because they help to explain improvement in the cardiovascular status of patients in whom the blood pressure levels are not significantly lowered following splanchnicectomy

EFFECT OF SPLANCHNICECTOMY UPON MORTALITY RATES

Because of the evidence of improvement in the cardiovascular status or the slowing of the rate of progress of cardiovascular disease in many patients for long periods of time following splanchnicectomy it seemed reasonable to expect that the operation would have a significant effect upon mortality rates as judged by a comparison with those patients similarly studied during the same period of time but who have never been operated upon Data bearing upon this question are summarized in Table 2 In Table 2 the mortality rates for all patients originally studied 10 to 20 years ago are calculated at the end of 10 years The patients are divided into four groups according to the amount of cardiovascular disease present when they were first seen A method of grouping which I have previously described was used[2] The patients are further divided according to sex and also according to whether they were operated upon or not The mortality rates are much lower in the patients who were operated upon Table 2 also deals with the statistical significance of the differences observed There can be no doubt that splanchnicectomy has prolonged the life of many hypertensive patients significantly

A COMPARISON OF THE EFFECT OF MEDICAL AND SURGICAL TREATMENT ON MORTALITY RATES IN SEVERE HYPERTENSION

Because the newer hypotensive drugs have been available for only a comparatively short period of time there is little evidence as yet of the effect

TABLE 3 COMPARATIVE FOUR YEAR MORTALITY RATES FOR GROUP III PATIENTS (SMITHWICK GROUPING)

AUTHOR	TREATMENT	NO CASES	MORTALITY
Smithwick	Nonsurgical controls	59	58%
Smithwick	Splanchnicectomy	115	19%
Perry and Schroeder	Hexamethonium and hydralazine	77	10%

TABLE 4 COMPARATIVE FOUR YEAR MORTALITY RATES FOR GROUP IV PATIENTS (SMITHWICK CLASSIFICATION)

AUTHOR	TREATMENT	SEX	NO CASES	MORTALITY
Smithwick	Nonsurgical controls	Males	79	94%
		Females	40	75%
Smithwick	Splanchnicectomy	Males	95	48%
		Females	44	43%
Perry and Schroeder	Hexamethonium and hydralazine	Males	58	50%
		Females	70	37%

of drug therapy upon mortality rates Recently Perry and Schroeder[3] published data on four year mortality rates for severe hypertensive patients who prior to treatment were in groups III and IV according to my method of classification *They compared their mortality rates with mine for the same* groups treated by splanchnicectomy and with my unoperated control patients as well The latter did not receive intensive drug therapy Perry and Schroeder s patients received both hydralazine and hexamethonium Their results are comparable to those following splanchnicectomy there being no statistical difference in the two series for this short period of observation The data are summarized in Tables 3 and 4 There can be no doubt about the fact that intensive drug therapy can lower mortality rates significantly *It seems reasonable to believe that combined medical and surgical treatment* will prove to be the best way to handle the more refractory cases and may prove to be the treatment of choice for many young severe hypertensive patients As indicated by Table 5 the percentage of patients who respond to chlorothiazide following splanchnicectomy compares favorably with the percentage of unoperated cases responding to chlorothiazide combined with other drugs The magnitude of the response is also the same The size of the dose of the drug is very much smaller in the patients who were operated upon I think a conservative estimate would be that at least 80 per cent of severe hypertensive patients can be controlled by splanchnicectomy alone or combined with small quantities of drug therapy for long periods of time

SOME EXAMPLES OF THE LONG RANGE (10 TO 20 YEARS) MANAGEMENT OF SEVERE HYPERTENSION BY SPLANCHNICECTOMY ALONE OR COMBINED WITH DIETARY OR DRUG THERAPY

As indicated previously we have found splanchnicectomy to be helpful in the management of patients who are refractory to medical management who will not follow a medical regimen or who can be controlled by drug

TABLE 5 RESPONSE OF HYPERTENSIVE PATIENTS TO CHLOROTHIAZIDE ALONE AND WHEN COMBINED WITH OTHER DRUGS OR WITH SPLANCHNICECTOMY
B P Response 1 to 14 Months

TREATMENT	NO CASES	% RESPONDING	AV REDUCTION IN B P
Chlorothiazide alone	48	48%	19/10
Other antihypertensive drugs + chlorothiazide	162	79%	35/21
Splanchnicectomy + chlorothiazide	43	77%	39/20

SURGICAL TREATMENT OF HYPERTENSION

(File No 13 57)

Dec 1944

LDS
R 8 I
L 8 I

PREOPERATIVE DATA		14 YEARS POST OP
W S M ♂ Age 48 Group 3		Age 62
204/104 298/154	Blood Pressure	174/98
4	Eyes	2
+	ECG	+
++	Heart Size	+
++	Heart Failure	0
25 70	P S P	28% 15 min
150/100	Sedation	

Diuril 125 250 mg/d

BLOOD PRESSURE mm Hg: 300, 275, 250, 225, 200, 175, 150, 125, 100 (right-hand marks: 140, 90)

Treatment SPLANCHNICECTOMY NORMAL DIET DIURIL

YEARS: 0, 2, 4, 6, 8, 10, 12, 14

Fig 2

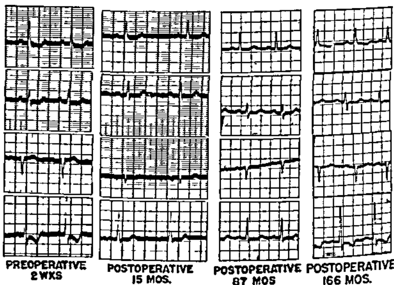
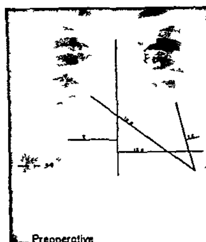


Fig 3

therapy but only with troublesome side effects Figures 2 3 and 4 concern a 48 year old male patient with malignant hypertension grade IV eyes severe congestive heart failure and good kidney function when first seen He was a district attorney and a dynamic driving type of person He could not and would not follow a medical regimen The course of his blood pressure following splanchnicectomy as judged by occasional follow up examinations by us on the ambulatory basis is illustrated by Figure 2 Although



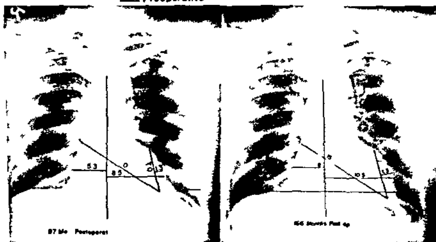


Fig 4

the levels over a period of 14 years compare reasonably well with the lowest preoperative values his blood pressure was never under satisfactory control Nevertheless he continues in good health and is still active in his profession His eye grounds are improved as are the electrocardiogram and heart size and function His renal function is still normal He was totally incapacitated at the time of operation The result almost certainly would have been better had he reduced his salt intake or could splanchnicectomy have been supplemented by one of the milder antihypertensive drugs He has recently agreed

to take small quantities of chlorothiazide in connection with a normal sodium intake We hope to be able to control his hypertensive cardiovascular disease for some years to come A number of electrocardiograms are shown in Figure 3 and films to show his heart size over the period of observation are shown in Figure 4 This patient illustrates what we have seen a great many times namely a slowing of the progress of cardiovascular disease and even the reversal of changes originally present in patients whose blood pressure levels have never been what one would like to see them during a follow up period of many years after splanchnicectomy

Figure 5 is a rather dramatic illustration of the satisfactory control of severe hypertension in a 24 year old female patient over a period of 19

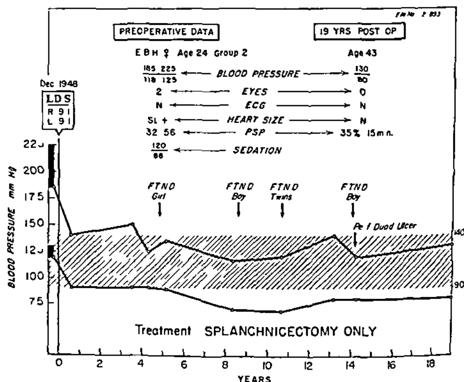


Fig 5

years Her blood pressure levels have always been satisfactory so dietary or drug therapy has not as yet been necessary It may well be in the future since she is now only 46 years old Our aim is a normal life expectancy if possible so we have about 30 years still to go It is theoretically possible that this result could have been achieved by modern medical therapy I have selected this patient as an example of many others referred to years ago by Newell and myself[4] who have had successful pregnancies following splanchnicectomy for severe hypertension with cardiovascular changes prior to pregnancy This woman has had four successful pregnancies and has five children because of one set of twins She went to the well once too often however because two months after her fifth child was born she was successfully operated upon for a perforated duodenal ulcer

Figure 6 is an example of the manner in which medical and surgical treatment can be combined to the interest of the patient Although I have emphasized that the hypertensive problem is greater in males than in females I am selecting another female as an example This 32-year-old woman had severe hypertension with ominous cardiovascular changes Prior to operation she had had three pregnancies all uneventful with living children By contrast with the case illustrated in Figure 5 the response to sedation was poor This usually means a form of hypertension which is more refractory to treatment. The blood pressure levels were reasonably satisfactory for

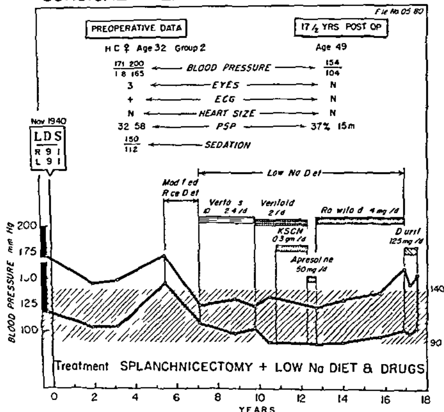


Fig 6

the first three years after splanchnicectomy From the fifth year on supplementary medical treatment in the form of low sodium diets combined with conservative drug therapy has been employed Now more than 17 years after operation her blood pressure is under satisfactory control on a normal diet and small doses of Diuril Her cardiovascular status is improved over what it was prior to operation

SUMMARY

Experiences with splanchnicectomy for hypertension over a 25-year period lead me to believe that it frequently slows the progression of or reverses

established cardiovascular changes It definitely increases the life expectancy of hypertensive patients

Splanchnicectomy is clearly indicated in the management of hypertensive disease which will not respond to medical management in patients who can not or will not follow a medical regimen or when medical management even if effective is attended with disabling side effects In my opinion conservative splanchnicectomy combined with supplementary medical treat ment as needed is a satisfactory way to control severe hypertension and hypertensive cardiovascular disease for long periods of time

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Sympathetic Ganglionectomy Results of Treatment*

KEITH S GRIMSON AND JOHN E W BAAY

Duke University School of Medicine

The removal of segments of the paravertebral sympathetic ganglia and chains for hypertension was pioneered by Adson[1] and Peet about 1935 and Smithwick[3] in 1939 Their operations were planned to effect sympathetic denervation of the abdominal viscera and varying portions of the lower body Poppen[4] and others have since modified these procedures to include additional upper midthoracic ganglia These procedures are generally referred to as thoracolumbar sympathectomies or splanchnicectomies Usually they do not include removal of the upper thoracic and stellate ganglia or the celiac and peri aortic mesenteric ganglia

Experimental studies between 1935 and 1940 demonstrated certain inadequacies inherent in splanchnicectomy and led to the belief that sympathectomies for hypertension should regularly include the stellate and upper thoracic ganglia, also the celiac and peri aortic mesenteric ganglia in addition to the usual splanchnic sympathetic chains This operation was first performed in 1940 and reported in 1941 by Grimson[5] It utilized a trans

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thoracic approach and included the stellate and 12 thoracic ganglia the splanchnic nerves and most or all of the celiac ganglia the upper lumbar or infrequently all of the lumbar ganglia It was called total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy It is often referred to as "total" sympathectomy In addition to the area of the usual thoracolumbar splanchnicectomy it included denervation of the upper body arms and head also the viscera of the thorax This upper area of denervation is characterized by a bilateral Horner's syndrome which patients do not mind and a relative bradycardia probably an important added benefit

It is appropriate for this Hahnemann Symposium that Dr Smithwick represent those who do splanchnicectomies that the results of "total" sympathectomy be given and that these results be compared with those of bilateral adrenalectomy[6] and combined splanchnicectomy and subtotal adrenalectomy[7] Interest in adrenalectomy alone or in combination with splanchnicectomy dates back seven or eight years It is therefore possible to consider the five year results of all groups Only the splanchnicectomy and the total sympathectomy groups can be reported at 15 or more years These follow up periods are shorter than those of several medical studies of the natural history of hypertension Therefore it should be emphasized that the surgical reports usually date from time of surgery and not from time of known onset of hypertension Also patients are selected by occurrence of signs or symptoms of impending difficulty while receiving adequate medical treatment

The experimental studies leading to "total" sympathectomy began in 1935 They were described by Grimson Wilson and Phemister[8] in 1937 and by Grimson[9] in 1941 It was demonstrated that a decline in blood pressure followed complete sympathectomy in dogs but that restoration occurred within six months Bradycardia and a decrease in cardiac output followed total sympathectomy and persisted beyond the stage of recovery of blood pressure Partial sympathectomy in the form of splanchnicectomy or upper thoracic and stellate ganglionectomy did not lower pressure Total sympathectomy blocked the acute hypertension occurring with lethal sustained increase of intracranial pressure Splanchnicectomy or upper thoracic sympathectomy alone did not prevent this maximum terminal increase of blood pressure * Preganglionic sympathetic nerve regeneration was demonstrated The importance of regeneration to any outlying sympathetic ganglia was emphasized Also in dogs it was demonstrated that total sympathectomy prevented or abolished the chronic elevation of blood pressure or neurogenic hypertension which follows section of the modulator or depressor nerves with excision of the carotid sinuses Splanchnicectomy or upper thoracic sympathectomy did not prevent alter or abolish chronic neurogenic hypertension Dogs with total sympathectomy were able to live and exercise without any significant disability

All of these studies lead to the belief that the paravertebral sympathetic ganglionated chains and all accessible outlying ganglia should be removed as completely as possible in man for the desired interruption of vasopressor pathways and in order to minimize effective regeneration There is no evidence that regenerating preganglionic nerves can activate adrenergic end organs or neuro-effectors unless they reach outlying sympathetic ganglia

* Subsequent studies have demonstrated that the pressor response to increased intracranial pressure although reduced, is not prevented by ganglion blocking drugs

and activate intact postganglionic neurons Such ganglia are numerous after most splanchnicectomy procedures in man Fragments or isolated ganglia are also present after "total" sympathectomy However, reduction of blood pressure moderate postural hypotension and bradycardia have persisted Patches of sweating on the trunk and extremities eventually develop in all patients but this is evidence of cholinergic regeneration through isolated ganglia or directly to cholinergic neuro-effectors

The technique of operation in man was described in detail in 1941[8] It is performed in two stages separated by an interval of three weeks At each stage the patient is placed in a lateral position and two incisions are made The first is through the third rib bed to expose the upper thoracic cavity and remove the stellate and upper seven thoracic ganglia The second is through the tenth rib bed to expose the lower thoracic cavity and permit removal of the lower five thoracic ganglia Through this incision the celiac ganglion is identified by traction on the greater splanchnic nerve and removed by spreading the fibers of the diaphragm Also the upper two or the fused upper lumbar ganglia are removed by downward retraction of the base of the diaphragm with separation of some of its posterior attachment The thoracic cavity is drained routinely for one or two days after operation

Postoperative neuritis like pain is occasionally troublesome for the first week and can persist several months This is best managed by careful explanation before operation by cheerful reassurance afterward and by use of salicylates and sedatives Narcotics are used for only a week after operation Avoidance of sympathy and concern by professional personnel and avoidance of any local anesthetics nerve blocks or other doubtful therapeutic procedures are an important part of the reassurance During operation the intercostal nerves are excised at the site of each excision of a rib segment A few patients in 1940 and 1941 had removal of all of their lumbar ganglia This did cause troublesome postural hypotension Since there is no known major hypertensive mechanism in the legs subsequent operations have left the third and fourth or lowest fused lumbar ganglia intact This leaves vasoconstriction in the legs and prevents disabling postural hypotension Actually my experience with thoracolumbar splanchnicectomy in about fifty patients is that they had more troublesome postural hypotension than follows "total" sympathectomy with the third lumbar ganglia left in place Also splanchnicectomy patients when standing have compensatory vasoconstriction in the upper body sweating and tachycardia These symptoms do not occur after "total sympathectomy With few exceptions a moderate and asymptomatic postural hypotension has persisted to the present time in the "total sympathectomy patients Also with few exceptions these patients have regularly continued with their work as business men laborers or house wives A few have become mothers or fathers although pregnancy is not recommended

The results of "total" sympathectomy in the first 172 patients were described in 1953[10] and compared with the then available follow up reports describing results of splanchnicectomy and available medical reports concerning untreated hypertensive patients The comparison was favorable In the 1953 report the reduction of supine blood pressure to near normal values below 150/90 was described as persisting in one third of the patients This is still true At the present time one third of the patients persist with reduction to near normal one third have definite reduction but not to normal

and one third have no significant reduction However with few exceptions this third have the usual asymptomatic and probably beneficial postural hypotension and bradycardia

For the present report the current survival of the "total sympathectomy patients who had operation more than five years ago has been ascertained There were 174 patients including a few of the seriously ill original ones who had markedly diminished renal function or intractable encephalopathy and would now be considered as having a contraindication to surgery Altogether seven patients died during the hospitalization for operation an operative mortality of 4 0 per cent Causes of death were the usual complications of hypertension This leaves 167 patients who survived operations performed five or more years ago Of these 21 died before five years a five year survival rate of 87 5 per cent There were 127 patients whose operations were performed ten or more years ago Of these 15 had died within the first five years and 16 by ten years a ten year survival rate of 75 5 per cent There were 28 patients whose operations were performed fifteen or more years ago This group naturally included the same number but now a higher percentage of the poorly selected original patients Of these 28 11 died in the first ten years and three more in the next five a 15 year survival rate of 50 per cent The survival rates at five ten and 15 years compare most favorably with those of any reports familiar to us and seem to justify use of total sympathectomy

Our patients have not been grouped according to one or another of the new classifications of hypertension Most classifications omit important relevant data such as heredity blood cholesterol weight temperament occupations and even age sex or race They can be considered at best as attempts in the right direction at worst as arbitrary and misleading The 1953 report on 172 patients did group them according to the Keith Wagener classification There were no grade I patients Twenty or 11 6 per cent were grade IV 48 or 27 9 per cent were grade III and 104 or 60 5 per cent were grade II It is emphasized that the 174 patients now considered for five ten and 15 year survival rates did not include individuals with severe myocardial infarction or cardiac failure requiring digitalis Of the 174 120 were female and 54 were male Ages varied from 14 to 51 average 35 3 years All had moderately severe to severe hypertension at the time of surgery All had been recommended for surgery by referral or in consultation by Dr Alf Alving of the University of Chicago or by Dr Edward S Orgain of Duke University School of Medicine

DISCUSSION

Total" sympathectomy has proved a satisfactory surgical means for treatment of moderately severe to severe forms of hypertension in patients under age 50 and without azotemia intractable increase of intraspinal fluid pressure cardiac failure requiring digitalis or severe emotional disturbance particularly alcoholism or drug addiction Benefit has been best evidenced by survival rates relief of symptoms and continuation at or return to regular work Benefit has also been evidenced by reduction of supine blood pressure to below 150/90 in one third and definite reduction but not to normal in another third These patients usually have not received post operative treatment Usually they have continued without medical control

between annual or occasionally less frequent hospital examinations Rehabilitation and long survivals also have been encouraging in the remaining third who had postural reduction of blood pressure but no significant lowering of supine readings This third of the patients often received medication with or without dietary restriction after surgery In general the results of surgery have not been dependent upon continuing patient cooperation and use of antihypertensive medication

It seems logical to recommend total sympathectomy for young patients with progressive hypertension who otherwise would have to continue a lifetime use of medication and diet Also total sympathectomy might be recommended for those in their forties who seem unable or unwilling to follow medicinal and dietary programs Once treated by this operation their benefit would continue Other eligible patients might be offered surgery for added protection Today we should be looking optimistically toward a normal life expectancy for people with hypertension For this objective the low fat diet at least and mild or occasionally troublesome antihypertensive medications might well frequently follow surgery Perhaps failure of medical treatment should no longer be a prerequisite to a decision for surgery Drugs and diets without surgery have yielded much improved results but surgery should not be delayed too long Patients partially benefited by diet and modern drugs during years of treatment may develop arteriosclerotic and other complications which would then contraindicate surgery or limit the chances of benefit Instead of failure of medical treatment it might be well to consider needed adjunct to medical treatment" or inability and unwillingness of the patient to continue medical treatment as prerequisite to surgery

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Adrenalectomy *versus* Sympathectomy Results of Surgery

HAROLD A ZINTEL
St Luke s Hospital New York City

As the title suggests this presentation is concerned with a comparison of the three to seven year results of two types of surgery in the treatment of patients with advanced essential hypertension Progress reports of these two series of patients have been published at intervals over the past few years[1 30]*

In 1947 when I first became interested in the surgical management of the patient with essential hypertension it was impossible to make direct valid comparisons of the data published in the literature on the end results of the various types of treatment of essential hypertension as reported by various authors The literature at that time was voluminous but the meaningful reports of the results of surgical and medical therapy could be counted on the fingers of the hands At that time each author had an original method of classifying the degree of severity of essential hypertension with the result that the data of one report could not be compared with the data of another report I am sure we will all agree that there is a very wide range of severity of hypertension Some patients have a mild elevation of blood pressure and no symptoms or evidences of organic damage while other patients with or without symptoms have severe and widespread organic damage We will all agree that efforts to treat hypertensive patients will be most successful in those patients with the least organic damage

In 1947 I was determined to operate upon a number of patients who had been studied extensively preoperatively and to follow them carefully over a number of years postoperatively It was my hope that after several years a classification of the severity of disease in these patients would have been accepted The data of our patients have been kept in special folders in the clinic on the patients hospital charts and on punch cards so that we might easily convert the classification of the patients to a standard classification method at any time Unfortunately to the best of my knowledge such a classification has not been accepted and is not in general use For this reason I find myself in much the same dilemma as I found myself in 1947 One cannot readily compare the results of therapy as reported in the literature regardless of whether the therapy was medical or surgical

* Several of the coworkers on this project over the years are contributors to this Symposium on Hypertension namely Drs William S Blakemore J H Hafkenschiel W A Jeffers A M Sellers and Charles C Wolferth Sr Other co workers include Drs A I Sutnick M A Lindauer J A Mackie S B Langfeld A G Hills and David W Parsons

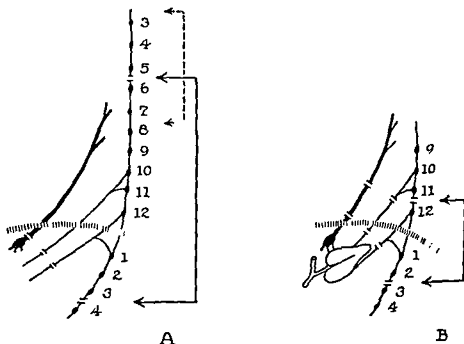


Fig 1

I would like again to make a plea for the adoption of such a standard classification system Once having adopted such a system and requesting all serious students of the subject to report their data by means of the system we could then readily compare one type of therapy with another or the results of one author with those of another Such uniform systems of reporting have been established for other fields of medical interest including the functional status of patients with valvular heart disease prior to surgery of the heart and the extent of carcinoma of the cervix prior to therapy by ir radiation or surgery When the classification systems were adopted in these fields the subsequent reports in the literature became considerably more meaningful Prior to the adoption of these classifications of severity of disease the interpretations of the end results were quite chaotic When such a uniform classification system is adopted in regard to patients with essential hypertension we indeed shall have made an advance in our understanding of this disease and the effects of our therapeutic efforts Also in the reporting of the effectiveness of any type of therapy it is important that all authors state how many patients were initially treated and also indicate how many patients *could* not *would* not or simply *did* not follow the prescribed therapy

In order to simplify the discussion of the patients subjected to operation by us those who had thoracolumbar sympathectomy with splanchnicectomy

TABLE 1

	"SYMPATHECTOMY"	ADRENALECTOMY
Number of patients	114	116
Average follow up in years	4 75	4.2

TABLE 2 SMITHWICK CLASSIFICATION

GROUP	SYMPATHECTOMY	ADRENALECTOMY
I	2	0
II	38	31
III	19	31
IV	55	54
Total	114	116
Average	3 11	3 20

–T6 L3 inclusive–will be referred to in this presentation as the patients treated by sympathectomy or as the "sympathectomized" patients Those patients who had a more limited sympathectomy–T12 L2 inclusive with division and removal of a segment of each of the three splanchnic nerves bilaterally and 90 to 100 per cent removal of all adrenal tissue–will be referred to as the adrenalectomized patients or the patients treated by "adrenalectomy" (Fig 1)

There were 114 "sympathectomized patients and 116 adrenalectomized" patients (Table 1) Seven of the patients who had an unsatisfactory response to sympathectomy were later subjected to adrenalectomy We have continued to use Smithwick s classification or grouping method to indicate the severity of the disease The two series of patients are quite comparable for the average Smithwick grouping of the "sympathectomized patients was 3 11 and the average for the adrenalectomized patients was 3 2 (Table 2) It should be noted that almost half of each of these two series of patients were in group IV There were 55 group IV patients among the 114 "sympathectomized" patients and 54 group IV patients among the 116 "adrenalectomized patients It should be emphasized that some surgeons feel that group IV patients should not be operated upon because of the advanced stage of the disease Patients who made good recoveries over a six month period following coronary occlusions and cerebrovascular accidents were included in these series The average age of the sympathectomized" patients was 41 years and the average age of the "adrenalectomized patients was 44 years Table 3 shows the age by decades of the patients living and dead of the two series of patients

The criteria used for the selection of these patients for operation have remained essentially unchanged since previous reports These include (1) severe disease as measured by diastolic pressures of 120 mm Hg or greater (2) evidence of progressive vascular damage to the brain heart eyes or kidney (3) failure to respond to vigorous medical therapy (4) age of not

TABLE 3 AGE OF PATIENTS

AGE (Years)	SYMPATHECTOMY		"ADRENALECTOMY	
	Living	Dead	Living	Dead
10–19	1	–	1	1
20–29	8	2	6	2
30–39	21	7	11	5
40–49	48	12	44	18
50–59	5	10	17	11
Total	83	31	79	37
Average	41 Years		44 years	

more than 55 years and (5) no vascular accident to the brain or heart within the past six months Initially those with advanced renal failure were accepted for operation but it was soon learned that these patients did not respond favorably Subsequently we have considered contraindications to either operative procedure phenolsulfonphthalein excretion of less than 15 per cent in 15 minutes and a blood urea nitrogen consistently above 20 mg per cent

In the sympathectomy group if no patient with a blood urea nitrogen over 20 had been operated upon the operative mortality and five year post operative mortality would have been reduced by 60 per cent In other words more than half the patients who died during the 30 day operative" period and since operation had abnormally high blood urea nitrogen levels Need less to say during the latter part of this study we were most careful in our attempt to select only those patients who had essential hypertension and to exclude those patients who had hypertension secondary to other disease conditions including primary renal disease

Those patients who in our opinion had such a low degree of mentality that they could not be relied upon to realize the necessity of daily steroid replacement therapy were excluded from the adrenalectomy series The number of patients excluded for such reasons is not known but probably there were not more than two or three It is of course important that the

TABLE 4 BLOOD PRESSURE RESPONSES THREE TO SEVEN YEARS

GROUP AND MAXIMUM INCLUDED BLOOD PRESSURE	PERCENTAGE OF LIVING PATIENTS OBSERVED			
	Sympathectomy"		Adrenalectomy	
A 150/100	37	68	55	80
B 180/110	31		25	
C 200/120	20	32	5	20
D No maximum	12		15	

The blood pressures used were the maximum blood pressure values usually the pressures obtained in the supine position The postoperative blood pressure responses were best in the adrenalectomized" patients

adrenalectomized" patient the immediate members of his family and the family physician realize the necessity for continued adrenal replacement therapy and the necessity for increased replacement therapy during certain periods of stress During the period of follow up of this report only one death in 176 patients subjected to 90 to 100 per cent adrenalectomy could be attributed to adrenal insufficiency

BLOOD PRESSURE RESPONSE

The blood pressure responses three to seven years postoperatively have been arbitrarily separated into four groups A B C and D The postoperative blood pressures recorded are the supine pressures which ordinarily are the highest pressures however if the standing pressures were higher the standing pressures were used An A postoperative blood pressure response is equivalent to 150/100 mm Hg or less The maximum pressures for groups B and C were 180/110 and 200/120 respectively and group D includes all patients with postoperative pressures over 200/120

TABLE 5 CARDIAC EFFECTS FOLLOWING OPERATION THREE TO SEVEN YEARS

	SYMPATHECTOMY		ADRENALECTOMY	
	Improved	Worse	Improved	Worse
Electrocardiographic tracings	39	10	65	5
Heart size	36	8	41	1

Only the percentages of patients showing improvement or worsening in electro cardiographic tracings and heart size are shown in this tabulation The percentage of patients with or without abnormality and no change postoperatively have been omitted

The blood pressure responses of the living patients of the two series excluding eight patients of the sympathectomy series and two of the adrenalectomy series on whom data were not available at the three to seven year period are shown in Table 4 Thirty seven per cent of the sympathectomized patients and 55 per cent of the adrenalectomized patients had a normal blood pressure response and 68 per cent and 80 per cent respectively had good blood pressures postoperatively—below 180 The average preoperative blood pressure of the initial 76 patients in the "sympathectomy" series was 218/135 Thirty two per cent of the sympathectomized patients had a poor (C or D) response with systolic pressures above 180 as compared to 20 per cent poor responses for the "adrenalectomized" patients

CARDIAC EFFECTS

The cardiac changes postoperatively have been evaluated by the use of electrocardiograms and orthodiagrams as well as by symptoms and indications of congestive failure and angina pectoris (Table 5) Excluding 14 patients on whom data were not available in the sympathectomy" series the surviving "sympathectomy patients showed improved tracings in 39 per cent and worse in 10 per cent Likewise excluding five patients in the adrenalectomy series 65 per cent were improved and only 5 per cent worse by this criterion In regard to heart size (Table 6) again excluding 17 of the sympathectomized and six of the adrenalectomized patients 36 per cent of the "sympathectomized patients had a decrease in heart size whereas 8 per cent had an increase in heart size and of the "adrenalectomized patients 41 per cent showed a decrease and 1 per cent showed increase in heart size In Table 5 the patients with or without cardiac abnormalities preoperatively and no change postoperatively are not included but were of course included in the calculation of the percentages

Among the 24 patients who required digitalis preoperatively only 19 required digitalis after "sympathectomy" Only one of the 35 patients who

TABLE 6 PATIENTS REQUIRING DIGITALIS

OPERATION	PREOPERATIVELY	POSTOPERATIVELY
Sympathectomy	24	19
Adrenalectomy	35	1

required digitalis preoperatively required digitalis after adrenalectomy (Table 7) Improvement of angina pectoris occurred in 16 of 19 patients treated by sympathectomy Three patients who did not have angina before developed angina after "sympathectomy After "adrenalectomy" only two of 17 patients continued to have angina

OTHER CHANGES

Following either procedure headache has disappeared in almost all patients and has become less troublesome in the several remaining patients Only two sympathectomized patients and one adrenalectomized patient

TABLE 7 POSTOPERATIVE COMPLICATIONS

	"SYMPATHECTOMY	ADRENALECTOMY
Pleural effusion	69	6
Pneumothorax	31	12
Hemothorax	15	0
Hydropneumothorax	5	1
Pneumohemothorax	10	0
Atelectasis	8	7
Thrombophlebitis	11	8
Pulmonary infarction	3	3
Cerebral vascular accident (nonfatal)	4	11
Fever	2	8
Wound infection	3	16
Adrenal insufficiency (mild)	0	14
Azotemia	6	5
Myocardial infarction	0	3
Pneumonitis	2	3
Retroperitoneal hemorrhage (severe)	0	4
Hemorrhage from wound	0	3
Cardiac arrest	1	0
Empyema	1	0
Hemorrhage from inferior vena cava	0	1
Miscellaneous	19	18
Total	190	123

Complications and sequelae (occurring within 30 days of the operation) in 114 patients (228 operations) after sympathectomy and 116 patients (232 operations) after adrenalectomy There were fewer postoperative complications following adrenalectomy

were observed to have progressive retinal changes postoperatively There has been occasional slight evidence of improvement in renal function but we have observed no uniform improvement in renal function On the other hand obvious progressive deterioration of renal function seems to have been averted in the majority of the patients

Postural hypotension has been more persistent among the "sympathectomy" group Its recurrence more than six months after adrenalectomy is suggestive of impending adrenal insufficiency Raynaud s phenomena have been observed in both groups of patients during cold weather but are easily avoided by the use of loose-fitting warm gloves A small incidence of peptic ulcer and severe gastrointestinal hemorrhage has been noted in both groups The effect of steroid therapy upon the incidence and progression of peptic ulceration is being studied in the laboratory animal Skin pigmentation has been apparent in approximately 30 per cent of those patients having "adre

nalectomy" It cannot always be reversed by increasing the steroid replacement.

A comparison of the postoperative complications shows some differences of morbidity between the two operative procedures (Table 7) Because the diaphragm is separated and the chest opened widely in the operation of thoracolumbar sympathectomy hemothorax and hydrothorax are often encountered as complications It is evident that adrenal insufficiency was found only in those patients having adrenalectomy Hemorrhage following the second stage of "sympathectomy" or "adrenalectomy" has been frequent enough to be a serious problem Persistent postoperative back pain has been a common complaint of most patients following thoracolumbar sympathectomy

TABLE 8 THE MORTALITY AND SURVIVAL OF PATIENTS WHO HAD "SYMPATHECTOMY" OR "ADRENALECTOMY" THREE TO SEVEN YEARS PREVIOUSLY

	"SYMPATHECTOMY	"ADRENALECTOMY"
Total Patients	114	116
Living	83 (73%)	79 (68%)
Dead (total)	31 (27%)	37 (32%)
Operative mortality	1 (1%)	6 (5%)

The similarity of the mortality among the two groups of patients is apparent Early in the series of patients with adrenalectomy replacement therapy and adequate blood replacement were not as well understood and may have accounted for some of these deaths
Survival less than 30 days postoperatively

The operative mortality (Table 8) for "sympathectomy" was 0 9 per cent and for "adrenalectomy" 5 per cent The number surviving thoracolumbar sympathectomy for three to seven years was 73 per cent and for "adrenalectomy" 68 per cent "Operative mortality" includes those who died in the hospital less than 30 days following an operative procedure Operative mortality in the "adrenalectomy" group was influenced by the inclusion of a number of patients who would not have been acceptable for "sympathectomy" The common causes of death are stroke coronary occlusion uremia and congestive heart failure Most of the "adrenalectomy" patients who succumbed died within two years following operation There appeared to be no such pattern among those who died following "sympathectomy" The causes of death are those seen commonly among patients with severe hypertension but there are no patients who died with congestive heart failure among the "adrenalectomy" group

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The Role of Sympathectomy and Adrenalectomy in the Management of Severe Arterial Hypertension

ALFRED M SELLERS WILLIAM A JEFFERS CHARLES C WOLFERTH, WILLIAM S BLAKEMORE AND MAURICE GOLDMAN

University of Pennsylvania

Historical Background The first attempt to utilize adrenalectomy in the treatment of hypertension was by Crile[1] in 1914 This was sixteen years before Pieri[2] performed resection of the abdominal sympathetics as treatment of hypertension In 1935 Adson[3] and Peet[4] described the sympathectomies subdiaphragmatic and thoracic respectively which now bear their names Smithwick began thoracolumbar sympathectomy clinically in 1938 and over the ensuing years the Smithwick type sympathectomy became the most widely used form of surgical treatment for hypertension

In our hands thoracolumbar sympathectomy was apt to be followed by morbidity with postural hypotension and backache In addition although it might relieve headaches caused by hypertension and halt the progression of retinopathy there was a not infrequent late recurrence of hypertension

Rationale of Adrenalectomy It has long been recognized that hypotension is one of the cardinal features of Addison's disease In addition if a patient with hypertension develops Addison's disease he may become hypotensive Hypertension may be restored in such patients by administration of desoxycorticosterone[6] There is evidence that the adrenal cortex may influence the formation of pressor substances and that formation of renin substrate hypertensinogen is deficient in adrenal cortical failure[7]

Adrenal steroids may increase reactivity of blood vessels to circulating pressor substances[8] Deane[9] described increased size of the adrenal zona glomerulosa and increased renin production in association with cellophane perinephritis Goldblatt[10] discovered that hypertension induced by clamping one renal artery could be abolished by adrenalectomy Increased size of the adrenals in hypertension has been described by pathologists[11 1 13]

Thus although there was no evidence linking the adrenal glands as initiators of the hypertensive process there was much to suggest that they played a major role in the maintenance of hypertension The availability of adrenal cortical replacement therapy in 1949 gave further impetus to consideration of adrenalectomy as an attack on the humoral mechanism of hypertension[14]

TABLE 1 TYPES OF OPERATIONS PERFORMED AND SURVIVAL TO PRESENT TIME

	OPERATED		SURVIVING		NO DATA*
Subtotal adrenalectomy alone	13		3		1
Subtotal adrenalectomy and Peet sympathectomy	1		0		
Subtotal adrenalectomy and Adson sympathectomy	65	168	42	111	1
Total adrenalectomy and Adson sympathectomy	88		61		2
Total or subtotal adrenalectomy and Smithwick sympathectomy	14		8		0
Total	181		114		4

* Refers to patients operated on less than six months ago and those in whom inadequate observations have been obtained during the past 12 months

Type of Operations Performed In Table 1 data are presented to include the types of operations we have performed and the survival rates from each Dr Harold A Zintel was in charge of the surgical aspects of this project from 1950 until 1954 The 13 patients subjected to adrenalectomy alone represented the first patients operated on many of whom had advanced renal disease with little hope of survival by any form of treatment then available From 1950 until the present 168 patients with severe arterial hypertension were subjected to total or subtotal adrenalectomy combined with Adson or Smithwick type of sympathectomy Attention is directed to these 168 patients who form a more homogeneous group for evaluation

Indications and Contraindications for Surgery Indications for surgical treatment of hypertension have included (1) failure to respond to adequate medical therapy (2) diastolic pressures of 120 mm Hg or more and (3) evidence of progressive vascular damage to the heart eyes brain or kidneys Surgery has not usually been attempted for patients over 55 years of age those who have suffered a myocardial infarction or cerebral vascular accident with less than six months convalescence and those with a blood urea nitrogen greater than 20 mg per cent or PSP excretion of less than 15 per cent in 15 minutes Emotional maturity and reliability were necessary requirements for those who were subsequently to depend upon adrenal replacement therapy

Duration of Observation Following Operation In Table 2 the duration of follow up of the 111 patients who have survived the combination of

TABLE 2 DURATION OF OBSERVATION OF 111 PATIENTS SURVIVING COMBINED ADRENALECTOMY AND SYMPATHECTOMY

Less than 6 months	2
6–12 months	8
1–2 years	5
2–3 years	11
3–4 years	12
4–5 years	20
5–6 years	23
6–7 years	16
7–8 years	13
8–9 years	1
Total	111

TABLE 3 SUMMARY OF MORTALITY 168 PATIENTS WITH COMBINED ADRENALECTOMY AND SYMPATHECTOMY

SMITHWICK CLASS	OPERATED	LIVING	DEAD	NO DATA	% SURVIVAL 6 MOS –8 YRS
II	58	51	6	1	88
III	43	27	16		63
IV	67	33	32	2	49
Total	168	111	54	3	

adrenalectomy (total or subtotal) and sympathectomy (Adson type 103 thoracolumbar sympathectomy 8) is presented Note the decrease in the number of operations performed during the past two years coincident with the availability of increasingly effective medical treatment

Mortality Of 168 patients subjected to combined adrenalectomy and sympathectomy 111 or 66 per cent have survived up to eight years after operation Fifty four patients have survived for five years or more Eight patients died within 30 days of the operative procedure and are classified as operative mortalities In Table 3 the over all mortality is presented in relation to the Smithwick classification as an index of the severity of the vascular disease existing in each patient prior to operation Of 58 patients in group II 51 are living and six dead Of 43 in group III 27 are living and 16 dead Among 67 in group IV 33 are living and 32 are dead This relatively high mortality in the group IV patients is not surprising when one considers that Smithwick[15] has not recommended surgery in this group of patients because of the advanced nature of their vascular disease The fact that we have had some excellent blood pressure responses in patients in this group is gratifying

There have been 22 deaths due to cerebral vascular accidents 15 due to coronary occlusions and six due to uremia (Table 4) Eleven others have died from causes unrelated to hypertension It is worthy of note that the deaths from uremia occurred in patients whose preoperative renal function was below the levels eventually established as adequate to permit surgery Congestive heart failure was not a cause of death in any patient However the occurrence of deaths due to vascular accidents in patients who have shown an excellent blood pressure response following operation has been a matter of concern to us It has re emphasized the interrelationships between hypertension and atherosclerosis in these patients As in the postoperative care of those having operations for the relief of degenerative vascular dis orders we have felt it desirable to include a low fat diet as an integral part of the over all management of these patients

TABLE 4 CAUSE OF DEATH

Stroke	22
Coronary occlusion	15
Uremia	6
Other	11
Total	54

TABLE 5 CLASSIFICATION OF RESULTS ACCORDING TO BLOOD PRESSURE

(A) Excellent	150/100 supine equal or less standing
(B) Fair	150–180/100–110 supine equal or less standing
(C) Poor	180–200/110–120 supine equal or less standing
(D) Failure	200/120 or more equal or less standing

RESULTS OF OPERATION

Blood Pressure Response In Table 5 blood pressures after operation are classified by an arbitrary system into A B C and D groups A indicating an excellent result and D a poor one[16] This classification of results does not allow for the degree of blood pressure fall from preoperative levels or for those responses which are present only when the patient is erect Fifty three per cent of those patients in the Smithwick group II 42 per cent of group III and 41 per cent of group IV had an (A) or excellent response Although the mortality in Smithwick group IV is high because of the advanced nature of the vascular disease it is noteworthy that 24 of the 35 surviving patients in this group have exhibited an (A) or (B) response (Table 6) Eighteen patients who now have an (A) or (B) response are receiving depressor therapy with improvement in blood pressure We have found that hypotensive responses to chlorothiazide[17] after sympathectomy and adrenalectomy may be dramatic operative failures occasionally may be converted into normotensive patients

The desired level of adrenal replacement therapy is based on the minimal amount of steroid required to maintain a state of well being without overt symptoms of adrenal insufficiency In the presence of renal insufficiency it has been our experience that the blood pressure usually will not fall until severe adrenal insufficiency occurs

Changes in Eyegrounds Recognizing that the goal of any treatment of hypertension is not merely the lowering of blood pressure but the delay or prevention of progressive vascular damage a true evaluation of the results of treatment must include data pertaining to important vascular beds affected by hypertension Among the 111 survivors of combined adrenalectomy and sympathectomy 13 were classified prior to operation as exhibiting grade IV hypertensive retinopathy with papilledema and 35 were classified as grade III because of retinal hemorrhages and exudates Among 100 of these same patients re examined during the past year none were found to show either grade IV or grade III changes In addition six patients now failed to show any retinal changes associated with hypertension All evalu

TABLE 6 BLOOD PRESSURE RESPONSE IN 111 PATIENTS SURVIVING COMBINED ADRENALECTOMY AND SYMPATHECTOMY

SMITHWICK GROUP	(A)	(B)	(C)	(D)	NO DATA
II	18	17	-	8	5
III	10	8	4	2	2
IV	12	12	4	1	6
Total	40 (2)	37 (16)	10 (2)	11 (8)	13
Per cent	36	33	9	10	12

The figures in parentheses indicate the number of patients receiving vasodepressor therapy

ations of the retinal vascular state were performed by members of the Ophthalmology Staff (Table 7)

Electrocardiogram and Heart Size Among the 111 survivors of the combined adrenalectomy and sympathectomy operation 92 exhibited an abnormal electrocardiogram prior to operation Electrocardiograms have been obtained during the past year in 94 of these 111 patients In 19 patients who exhibited a normal electrocardiogram prior to operation there has been no change Forty three patients have shown evidence of improvement in the pattern of left ventricular hypertrophy and 26 who had had electrocardiographic abnormalities prior to operation have shown no appreciable change Only six are regarded as being worse than prior to operation one because of right bundle branch block three because of myocardial infarction one *because of atrial fibrillation but only one because of increase in the changes* associated with left ventricular hypertrophy or the hypertensive state

Orthodiagrams were performed during the past year in 98 of the same 111 surviving patients Thirty five patients who had a normal heart size prior to operation are unchanged Twenty four with cardiac enlargement before operation remain the same and in 34 the heart size has decreased since operation In only two patients has the heart undergone further hypertrophy following operation

TABLE 7 CHANGES IN ELECTROCARDIOGRAM HEART SIZE AND EYEGROUNDS

	IMPROVED	NORMAL PREOP STILL NORMAL	ABNORMAL PREOP STILL ABNORMAL	WORSE
Electrocardiogram	43	19	26	6
Heart size	37	35	24	2
Ocular fundi	68	0	27	0

Congestive Heart Failure and Angina Pectoris Thirty six of the 111 survivors of combined adrenalectomy and sympathectomy presented evidence of heart failure prior to operation and 18 of these were sufficiently severe as to require digitalis Following operation relief from heart failure has been remarkable No patients present evidence of fluid retention and only three receive digitalis two of these for atrial fibrillation Improvement in signs and symptoms of congestive heart failure did not appear to be dependent primarily on reduction in blood pressure because in several patients relief appeared either in the absence of blood pressure response or before a fall in blood pressure occurred Studies made by Hills[18] in some of these patients suggested that increase in sodium excretion is probably the most important factor in helping to relieve congestive failure

Seventeen patients were subject to the anginal syndrome before operation and 12 of these are improved However, the fact that four patients have developed angina since operation has pointed out to us the necessity for directing treatment toward the atherosclerosis Improvement in blood pressure alone is not enough to insure against the development of coronary or cerebral atherosclerosis

Renal Function Preoperative evaluation of renal function was limited mainly to measurement of blood urea nitrogen and PSP dye excretion Following adrenalectomy the BUN became a less reliable index of renal function since most patients were maintained in a state of borderline adrenal

insufficiency Based on postoperative measurement of renal PSP excretion there appeared to be very little change in renal function Three patients whose PSP excretion prior to operation was less than 15 per cent in the first 15 minutes have had no further deterioration of renal function In addition only two patients have died of uremia beyond the first year after operation In three patients studied before operation by creatinine PAH and inulin clearance there is confirmation that renal function was preserved at the same levels seven or eight years after operation [19]

Headache Headache had been a major complaint prior to operation in 69 of the 111 survivors of combined adrenalectomy and sympathectomy In 65 the headache was relieved or disappeared entirely after operation Similar results have been observed after sympathectomy alone

Adrenal Replacement Therapy No adrenal steroid replacement is required during or after the first stage operation On the evening prior to the second stage totally or subtotally adrenalectomized patients receive 50 mg of cortisone intramuscularly On the day of operation 100 mg of cortisone are given intramuscularly four hours before operation and 50 mg are given eight hours postoperatively On the first postoperative day 25 mg of cortisone are given intramuscularly every six hours On the second and third postoperative days the patient receives 25 mg of cortisone every eight hours orally or intramuscularly By the fourth day the dose is cut to 25 mg of cortisone twice daily and thereafter a maintenance dose of 12 5 mg of cortisone three times a day is usually adequate if there is no fever or severe postural hypotension [0]

Florinef (9 alpha fluorohydrocortisone) a synthetic mineralocorticoid is begun on the second postoperative day in a dose of 0 05 mg once daily Because of the potent salt retaining effect of Florinef we rarely have had to give supplementary sodium chloride tablets but we do suggest liberal use of the salt shaker

Complications of Adrenalectomy The dosage of adrenal steroids used in the management of these patients represents replacement rather than therapeutic levels Therefore one should not expect to encounter the symptomatology usually associated with the administration of very large doses of cortisone Actually our suggested levels of cortisone administration were kept low as part of the principle that following adrenalectomy the minimal quantity of adrenal steroids should be given which was consistent with the patient s sense of well being One of the most troublesome problems encountered related to the appetite stimulating effect of cortisone The resultant *weight gain* often occurred in spite of our advice to follow low calorie diets and use anorexigenic drugs

Hypoglycemic Attacks Hypoglycemic attacks have occurred but fortunately have been uncommon These attacks did not respond to an increase in the frequency or amount of cortisone medication but rather to spacing of the feedings [1]

Skin Pigmentation Addisonian skin pigmentation was noted in 40 of the 111 survivors of adrenalectomy usually appearing within three months after the second stage operation Awareness of increased skin pigmentation usually occurred in the form of sun tan which lasted beyond the summer season Melanosis was more frequent in the Negroes than among the Caucasians It persisted in spite of administration of adequate doses of cortisone and in the absence of any other clinical evidence of adrenal insufficiency

Raynaud s Phenomenon Varying degrees of pain numbness and pallor

of the fingertips occurred in 27 patients upon exposure to cold. In only one instance did these complaints cause the patient to change his occupation. No treatment beyond the use of warm gloves has proved necessary. Although we have no good explanation for this phenomenon, hyperactivity of the upper thoracic sympathetic fibers following extirpation of the lower thoracic and lumbar ganglia may explain the symptoms in part. Why this complaint does not occur in all patients subjected to the same type of sympathectomy is not clear.

PEPTIC ULCER. Sixteen of the 168 adrenalectomy-sympathectomy patients have developed peptic ulcer while receiving cortisone replacement therapy, and 11 of these have bled. Unfortunately there have been three deaths associated with gastrointestinal hemorrhage. Careful history revealed that some ulcers at first thought to have been induced by steroid therapy existed before such treatment was started. Furthermore, it is difficult to assess the effect of emotional tension as a precipitant of gastrointestinal bleeding acting quite apart from the possible ulcerogenic effect of steroids. The natural incidence of peptic ulcer in the United States usually is estimated at 5 to 10 per cent.[20] The incidence of ulcer among the adrenalectomy-sympathectomy patients does not exceed these values.

ADRENAL INSUFFICIENCY. Patients subjected to *total* adrenalectomy have been maintained on an average of 37.5 mg. of cortisone and 0.05 mg. of Florinef daily. Following *subtotal* adrenalectomy it has been possible to maintain patients on as little as 12.5 to 25.0 mg. of cortisone, and many have felt well without steroid replacement, showing no evidence of adrenal insufficiency. With respect to their hormone requirement, the subtotally adrenalectomized patients resemble patients with Addison's disease in that some can subsist without exogenous hormone. However, both groups of patients lack the ability to increase the basal rate of adrenal steroid secretions.[18] It has been found necessary to increase the dose of steroid replacement in the operated patients when they are subjected to stresses such as acute infections and operations. Additional hormone has been given to all patients during the hot summer months as a safeguard against salt depletion due to excessive sodium loss in sweat. We have encountered 32 episodes of mild and 11 of severe adrenal insufficiency. One death due to adrenal insufficiency occurred in a patient who had an excellent blood pressure response but failed to follow our advice to contact his physician for treatment of acute bronchitis.

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Pneumothorax When the thoracic sympathetic ganglia have been removed pneumothorax should be anticipated during the first 24 hours after operation even though no pleural rent was visible at operation In our series [illegible] is been an infrequent but important complication One patient (D J) [illegible] observed to have developed a right hemiplegia with motor aphasia [illegible] the night following her second stage adrenalectomy and sympathec[illegible] A large left pneumothorax also had made its appearance As Dr Zintel [illegible] drew [illegible] from her chest her neurologic signs cleared completely It [illegible] interpreted that hypoxia from the pneumothorax had induced her [illegible] focal cerebral vascular insufficiency We have also observed that [illegible] pneumothorax can be responsible postoperatively for hypotension and [illegible] which cannot be reversed until the air is withdrawn In addition to examining our patients frequently we have routinely obtained portable chest x rays within four hours after operation to exclude this important complication

Pulmonary Edema This complication has arisen only once in our series as an immediate postoperative complication following sympathectomy and/or adrenalectomy We have tried to protect patients against it by the judicious use of digitalis and aminophylline Even more important, we believe have been our precautions against overloading the circulation with fluid during and after operation We have attempted to estimate blood loss at operation as accurately as possible [4] in order to allow prompt replacement without overloading the circulation Early errors of failing to transfuse sufficiently to overcome blood loss have resulted in more adequate replacement of blood despite the possibility of pulmonary edema

Vascular Accidents Where there have been symptoms prior to operation of angina or cerebral vascular insufficiency such patients have received special attention Our incidence of early postoperative complications in these areas has been small Two measures which appear to have been helpful in such patients are the use of oxygen for 48 hours after each stage and gradual ambulation begun only when it has been demonstrated that blood pressures do not fall to dangerously low levels as the patient sits in bed with legs dangling

SOME PROBLEMS OF THE LATE POSTOPERATIVE PHASE

Postural Hypotension Whereas a sharp fall in blood pressure immediately following operation is usually an ominous sign indicating hemorrhage a postural fall in blood pressure upon standing has not often been a disabling side effect of thoracolumbar sympathectomy or of combined adrenalectomy and subdiaphragmatic sympathectomy This postural hypotension is prone to prolong the convalescence of those having the Smithwick operation as compared with patients subjected only to subdiaphragmatic resections particularly if convalescence occurs during the summer months.

If the postural fall is not severe enough to produce temporary cerebral vascular insufficiency it may prove to be advantageous for those whose lying pressures remain high following operation Usually the orthostatic effect persists for not more than three months Hills[5] has pointed out that a L

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Some Early and Late Postoperative Problems in the Surgical Treatment of Hypertension

WILLIAM A JEFFERS M AUGUST LINDAUER ALFRED M SELLERS WILLIAM S BLAKEMORE FRANS J BARENDS AND CHARLES C WOLFERTH

University of Pennsylvania

It is the purpose of this report to record some of the lessons learned during our past 25 years experience in exploring the surgical treatment of hypertension The surgeons chiefly concerned have been in chronological order Drs Francis C Grant Norman E Freeman Harold A Zintel William T Fitts and William S Blakemore Dr I S Ravdin has been the chief surgical consultant Drs Wolferth Jeffers and Francis C Wood have been medical consultants throughout and Dr Joseph H Hafkenschiel Jr has contributed much Dr John H Moyer participated in the study for a year prior to his departure for Houston It is not feasible to acknowledge by name many others in the departments of Surgery Medicine Anesthesiology and Ophthalmology in the Hospital of the University of Pennsylvania who have participated in this work

It has been possible not only to develop surgical methods for the control of hypertension but also to carry them to completion with success and with a creditable morbidity and mortality as reported by Drs Zintel and Sellers in this Symposium As a by product of this study we have learned much concerning the ability of hypertensive patients to withstand major surgical procedures An outstanding contraindication to operation whether for the relief of hypertension or for another major surgical procedure has been *renal insufficiency* Other vascular impairments such as a prior stroke or a coronary occlusion do not usually present contraindications if adequate recovery from them is achieved before operation is attempted

The number of patients we have selected for operation has diminished progressively as new and increasingly effective medical measures have been discovered Only since 1957 in our opinion have these medical agents been developed to the extent that they challenge or supersede operation in the management of certain severely hypertensive patients without renal insufficiency Although we anticipate the discovery of increasingly more potent safe and effective medical measures a review of some problems encountered in connection with operations for the relief of hypertension seems timely Even if drugs can be shown to be more effective than sympathectomy and adrenalectomy[1,2] other types of operations must still be performed upon

patients with hypertension and the lessons we have learned will be applicable Furthermore as our diagnostic acumen improves the scope of surgical treatment of hypertension should expand Instead of performing operations to modify the course of essential hypertension we shall be able to diagnose and treat surgically with increasing success such specific causes as coarctation of the aorta cortical and medullary adrenal tumors and both vascular and infectious renal lesions

Because patients with *severe* hypertension present risks which make them ineligible for purely *elective* surgery we have felt it mandatory to know in advance of operation the complete medical background Not infrequently our patients have been known to us for months or years and have been selected for operation only when signs of progressive vascular damage gave evidence of our failure to control them by medical means Our acquaintance with them had allowed us to (a) exclude specific causes for hypertension (b) evaluate the severity of the hypertension with repeated postural blood pressure tests [3] (c) assess vascular damage in the eyes brain heart and kidneys and (d) reach a well considered conclusion regarding therapy Such information in advance of operation has allowed us to be alert to the specific vulnerabilities of our patients e g one with angina pectoris might be susceptible to a coronary occlusion When the internist surgeon and anesthesiologist have had this full knowledge of the patient the design of the operation and the postoperative management could be planned with some confidence

Patients with hypertension may be characterized in this fashion with respect to their operability (a) They will tend to bleed freely This tendency evidenced by epistaxis subcutaneous hemorrhages with or without trauma and a positive tourniquet test cannot be reversed by any medical agents now available Meticulous hemostasis at operation will therefore be required (b) Like patients with diabetes mellitus they must be suspected *of having suffered damage involving the small arteries of the brain* heart and kidneys (c) As a corollary to (b) they are subject to thrombosis or hemorrhage if wide fluctuations of blood pressure are allowed during or after operation They may also be vulnerable to pulmonary edema if excessive fluids are given Because of these hazards operations should be performed as expeditiously as possible but not to the extent that hemostasis is jeopardized

PROBLEMS OF THE EARLY POSTOPERATIVE PHASE

Hypotension Hemorrhage Although a stroke or coronary occlusion can give rise to hypotension immediately after operation the hypertensive patient who develops marked hypotension should be suspected of bleeding until proved otherwise Blood pressure must be restored promptly by the liberal use of transfusions and pressor amines including norepinephrine if necessary Occasionally exploration of the wound will be required to secure a bleeding vessel Even if other causes for hypotension subsequently become evident these initial restorative measures must be employed and should be instituted without delay where pressures fall as low as 120 mm Hg in a *patient accustomed to systolic* pressures in the range of 200 mm Hg Tachycardia and other evidences of shock will usually be associated It should be kept in mind that a fall in blood pressure is a *late* manifestation of hemor

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If the postural fall is not severe enough to produce temporary cerebral vascular insufficiency it may prove to be advantageous for those whose *lying* pressures remain high following operation Usually the orthostatic effect persists for not more than three months Hills[5] has pointed out that a late

return of postural hypotension in those who were subjected to adrenal resection is the first sign of impending adrenal insufficiency We have rarely found it necessary to use elastic stockings or abdominal binders for more than a few weeks following operation

Obesity and Its Implications We have usually rejected for operation those obese patients who have been unable to achieve substantial weight reduction as a part of a medical regimen Similarly we have tried to prevent postoperative patients from gaining weight excessively for fear that progressive atherosclerosis might occur Following adrenal resections this has been difficult since cortisone stimulates appetite The correction of obesity remains we feel an important objective both before and after operation

Major Surgery Following Operations for Hypertension It has been possible to operate upon our patients for subsequent urgently needed surgery Such operations have included hysterectomy subtotal gastrectomy radical mastectomy cholecystectomy and herniorrhaphy for strangulation Even among those who have had thoracolumbar sympathectomies there has been a tendency to develop alarming hypotension during and after further operations In those with adrenal resections combined with sympathectomy we have utilized steroid therapy in doses comparable with those used at the time of resection of the second adrenal[6] Despite this episodes of severe hypotension have occurred We conclude that our patients can at best be considered poor risks for operation For this reason occasional patients receiving steroid replacement therapy who have developed bleeding from peptic ulcers have as yet not been subjected to laparotomy but have been managed on only a medical program

Hypertension Persisting after Operation As Drs Zintel and Sellers have pointed out our percentage of those who fail to respond to operation has been small We have been successful in improving blood pressure levels in many of these failures through the use of depressor agents With the cautious use of chlorothiazide in combination with other depressor agents we have observed further improvement among those subjected to both thoracolumbar sympathectomy and adrenalectomy combined with sympathectomy The daily dose of chlorothiazide has not exceeded 750 mg Our current series includes five Smithwick patients whose pressures were 180/110 or higher prior to the addition of chlorothiazide All have since shown pressures not exceeding 160/110 *while standing* an orthostatic fall being apparent in four Among five patients subjected to *combined adrenalectomy and sympathectomy* followed by an unfavorable blood pressure response two now have essentially normal blood pressures with the addition of chlorothiazide Two others with pressures in the range of 175/115 have not responded to the addition of chlorothiazide 250 mg to their usual depressor regimen One has failed to respond to the addition of 500 mg of chlorothiazide daily

Adrenal Insufficiency and Related Problems Among those whom we have subjected to a combination of adrenal resection and sympathectomy episodes of acute adrenal insufficiency have been rare Only one patient has succumbed to this complication We have learned to increase replacement therapy during such stresses as acute infections and very warm weather or in preparation for subsequent surgical procedures It has been helpful to know that hydrocortisone 300 mg given each 24 hours as a slow intravenous

infusion has constituted complete steroid replacement therapy for the treatment of acute adrenal insufficiency

Other side effects of the combined operation include intolerance to cold Raynaud s syndrome involving the upper extremities pigmentation and failure of ejaculation These have not been serious complications among our patients

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Discussion

JOHN M HOWARD *Moderator*

WILLIAM BLAKEMORE	JOHN PETERS
ROBERT BOWER	ALFRED SELLERS
ALBERT BRUST	REGINALD SMITHWICK
KEITH GRIMSON	HAROLD ZINTEL
WILLIAM JEFFERS	

DR HOWARD Dr Smithwick would you begin by commenting on your classification of hypertensive patients?

DR SMITHWICK The classification that I have used divides patients into four groups My interest in this was stimulated by the Keith Wagner and Barker classification which as I recall was published in 1939 They attempted to divide hypertensive patients into four groups on the basis of

changes in the eyegrounds They followed 156 cases for five to nine years and at the end of that period of time they showed very clearly by survival curves that there was a highly significant difference in the length of life of these patients according to whether their eyegrounds were grade I II III or IV As I began to learn a little something about this disorder I realized that there were a good many patients who had grade III or IV eyegrounds whose prognosis was quite different from other patients who had identical eyeground changes with relatively minor changes in either the cardiac or the renal area Therefore I thought it well to take into consideration the cardiovascular system as a whole in developing the classification so we graded the cerebral changes into three categories and also electrocardiographic changes heart size and kidney function Taking all of these areas into consideration we divided the patients into four groups in which the eyeground changes alone were not the reason for putting them into the groups I tried to group similar types of patients as nearly as possible in each of these four categories It s really quite a problem to devise a system for dividing them into groups so that when we re talking about the results of treatment we re talking about patients that are as nearly comparable as possible

Dr Grimson Were I to use a classification in hypertension I would want to know the patient s heredity his weight recently his race sex and occupation I would want to know the personality make up of the patient and his wife his blood cholesterol level and whether he smokes I don t feel confident to take my patients and put them in any classification

Dr Sellers We have been grateful for the availability of Dr Smithwick s classification and have used it extensively in evaluating our patients both in drug studies and preoperatively so that we might then compare our results with those achieved elsewhere I d like to ask Dr Smithwick a question in regard to a statement he made as to whether or not patients who are in his grade IV classification should be considered as good candidates for operation I reason from this that because of the advanced nature of their vascular damage these patients would not tend to do well and you thought that possibly they should not be subjected to surgery

Dr Smithwick The most serious thing about the group IV patients is severe impairment of kidney function These patients generally have a very high resting diastolic pressure 130 or 140 If in addition they have a poor response to sedation you can predict with absolute certainty that it s too late not only for surgery but I m sure for surgery combined with every other therapeutic weapon we ve got The reason I ve not encouraged people to think of treatment surgical or otherwise in group IV patients is that while the prognosis is improved in general the results are bad by comparison with people in the other groups I like to encourage people to do something about it before they get into group IV and I think that really is the important consideration If you have a patient in group IV who has good kidney function but who is resistant to medical treatment he should certainly be operated on realizing that supplementary medical treatment will probably be needed There are many people in group IV who will profit from combined treatment

DR HOWARD I d like to go down the line and see what the panelists think they can achieve with sympathectomy The figures have been presented and they might not all be comparable but lets take a class of patients shall we say grade III and see what the five year survivals might be, first without surgical therapy and then with surgical therapy Is that a good postulate Dr Jeffers or would you propose a better one?

DR JEFFERS Thats a very difficult question I m afraid Dr Howard because we dont know how to define medical therapy Medical therapy has come up first Our standard of reference is surgical therapy in my opinion as we test new drugs I dont think we know enough about the long term effect of potent drug therapy to attempt to answer that question just yet

DR HOWARD How about the natural history—can we compare that with surgery? Yes Dr Grimson

DR GRIMSON I m sorry to interrupt but it so happens that since 1949 I have had 120 patients continuously on hexamethonium not changing from one drug to another but on continuous treatment I do not have the exact breakdown on five year survival rate or on reduction of pressure but I would say that medical management using that agent comes to within 70 per cent of the effectiveness of my own total sympathectomy The only draw back is that it s hard to keep the people taking it and those who drop off therefore lose the benefit You have to rely on the willingness of the patients and their continuing cooperativeness

DR HOWARD But you have added chlorothiazide more recently to some of those patients

DR GRIMSON Only if the patient is developing trouble and of course more recently we do the same with the surgically treated group

DR HOWARD Yes but the point I m making is that chlorothiazide and related drugs are important new agents I dont think we have enough perspective on the effect of combining the two to make an adequate comparison at this time

DR GRIMSON Well can we get any degree of comparison even within the surgical group?

DR ZINTEL When you re evaluate these patients year by year it s difficult to remember what new results were for a particular year and what the results of other people were

DR HOWARD Our audience is interested in whether sympathectomy and adrenalectomy are comparable and if not which is the better operation Lets compare sympathectomy and adrenalectomy after five years

DR ZINTEL We havent got five-year survival reports as yet but we are close to it and our figures were 58 per cent survival after sympathectomy and 72 per cent survival after adrenalectomy These are not statistically different

DR HOWARD If you were to treat a patient tomorrow what would you advise?

DR ZINTEL What we've always advised Those patients who have severe advanced hypertension who have been adequately treated by a competent internist who fail to respond to such therapy those patients should be subjected to surgery

DR HOWARD To what surgery?

DR ZINTEL I think I'd prefer adrenalectomy

DR BLAKEMORE As a general statement I'd agree with that There are exceptions when we don't recommend adrenalectomy These are first the patient who can't get good medical follow up and management in his local community and second the one who is not mentally competent enough and emotionally stable enough to continue on a substitution therapy after operation For these exceptions I think sympathectomy would be the answer

DR GRIMSON Are we in grade IV?

DR HOWARD Our panelists have shifted over to grade IV

DR GRIMSON In grade IV to me there are two groups There is the patient with minimal papilledema who has some hemorrhages and exudates but is not at the point of blindness from retinal deterioration His renal function is low but not to the point of azotemia This early malignant hypertension or early accelerated hypertension I think can well be treated with hexamethonium and Apresoline Years ago we treated these successfully with sympathectomy but the risk was high Now they can be converted to a more benign state and then given total sympathectomy as a lasting thing if we don't rely on their cooperation Drug therapy if effective can be continued in the cooperative patient The patient who is blind and has increased spinal fluid pressure or severe renal damage is strictly medical in my opinion and a great deal can be done for him today medically

DR SMITHWICK Well I'm sort of in the middle here There isn't any operation that's been done that I haven't done for hypertension but there are two operations that I have done very infrequently one is total sympathectomy and the other is total adrenalectomy Dr Grimson explained in the early part of his talk why he became interested in total sympathectomy I think it was an operation that had to be explored because there certainly was no effective medical treatment at that time It's a terribly radical operation and I have never done one in simply two stages The dozen or so that I did I did in multiple stages attempting to try to satisfy myself whether increasing the magnitude of the operation gave sufficient benefit to outweigh the increasingly disabling side effects of the more extensive maneuver I satisfied myself very quickly that in my opinion the untoward side effects of total sympathectomy far exceeded the benefits that were gained so far as the control of hypertensive disease was concerned Some of the patients that I operated on couldn't stand up for five years without girdles and stockings and were so incapacitated they couldn't work Under no circumstances

would I do a total sympathectomy in a human being regardless of how severe his hypertension is

DR HOWARD Dr Smithwick thats a definite statement Dr Grimson would you like to reply?

DR GRIMSON It seems to me that Dr Smithwicks operation is upside down mines right side up If a man needs vasoconstriction in the feet leave him the second and third lumbar If he doesnt want compensatory tachycardia and vasoconstriction in the upper body when he stands take it out Leave him right side up physiologically and hemodynamically

DR SMITHWICK With regard to total adrenalectomy if were going to take out the adrenal glands its better to remove them entirely and to depend on replacement therapy But we cant turn loose people with no adrenal glands on total replacement therapy except where theyre going to have available to them expert medical care They should be tagged and have a letter in their pocket stating just what should be done by any doctor who may have to take care of them

This symposium has dealt largely with newer drugs Certainly this is a great advance in the management of large numbers of hypertensive patients I believe that the need for the more radical operations has been greatly lowered I personally believe that a conservative splanchnicectomy which does not commit a patient to total replacement therapy or to the prolonged recovery period of a total sympathectomy is all that one should do at this time

DR JEFFERS I would first have to agree with Dr Smithwick in that when we send our adrenalectomy patients abroad we likewise insist on sending a packet of information along with them We give them a vial or two of injectable cortisone to take if necessary Although we too feared the metabolic consequences of this operation the difficulties have been far less than we had anticipated The reason we have pushed this operation is that it is a less extensive surgical procedure I would dare say that the reason why the Smithwick operation is not performed widely in this country at present is because there is only one Dr Smithwick It takes a lot of skill and a lot of careful management to carry patients through operations that extensive and for that reason Dr Zintel was glad to work out a procedure which is a lesser procedure in our opinion although its metabolic effects are more far reaching

DR BOWER Id like to ask Dr Grimson a question Im not quite clear about his selection of patients for total sympathectomy Is it true that you do not electively do a total sympathectomy now Dr Grimson? Is it only on those patients who you predict will not adhere to medical management?

DR GRIMSON The use of total sympathectomy as Dr Smithwick has mentioned is based upon medical failure Each of us can manage patients without much disability The reason that were doing fewer surgical procedures is that there are fewer medical failures For the first time in my life I know something that will predict the results of sympathectomy and it isnt any classification It is failure of medical treatment Failure of adequate medical

treatment predicts a poor result from sympathectomy almost always I've learned that in the last five years

DR ZINTEL All of the patients in the two series that I have mentioned were considered to be medical failures There were a few who were progressing so rapidly it was assumed that the patients wouldn't respond well to medical treatment These were all selected on that basis before they were referred to me for operation

DR HOWARD Dr Brust have they convinced you that operation alters the life expectancy of the patient with hypertension?

DR BRUST I think in follow up of the comments that Dr Grimson made emphasizing the individual variability of the patient we have to admit that the natural history of hypertension isn't natural at all It's a very unnatural thing A few years ago there was such great enthusiasm for the antihypertensive agents that there were many who felt that surgical therapy for hypertension was a thing of the past I think the presence of this panel here today indicates that the pendulum is beginning to swing back In terms of target organ involvement short of irreparable renal damage there is no question in my mind that extensive sympathectomy can dramatically produce reversal of these things I believe Dr Smithwick was one of the first to demonstrate that the more severe the pattern of left ventricular strain in the electrocardiogram the more likely one was to get a reversal of this pattern with sympathectomy The same thing has been demonstrated with respect to grade IV retinopathy And interestingly enough the grade IV retinopathy will go back to grade II retinopathy many times with sympathectomy whether the blood pressure is lowered or not

DR HOWARD Dr Sellers is the economic cost of support after adrenalectomy a major factor?

DR SELLERS The cost of the daily measure of replacement therapy for the average adrenalectomy patient runs from 25 to 30 cents which compares favorably with the patient who is taking three antihypertensive agents three or four times a day The antihypertensive drugs may cost as much as a dollar or more per day

DR HOWARD Is there agreement on which patients should have surgery for essential hypertension? Would each panel member express himself as to whether he thinks 1959 or 1960 will see an upswing in the volume of surgery done in the treatment of hypertension? Dr Peters?

DR PETERS As one interested primarily in research and going forward I would naturally prefer to believe that in 1959 1960 or 1961 we would have reached a point where anything that is traumatic anything that carried a mortality of any degree could be obviated by either our discovering the basic etiology or discovering an economically feasible and easily administered medical therapy On the other hand I would guess from the trends of the discussion here today that at least temporarily we've reached a point where perhaps because of the new drugs and a clearer definition of their

limitation with more experience, there's going to be an upswing in surgical therapy

DR BRUST In terms of the type of patient who should be considered for surgery it seems rather apparent from the previous essayists on this panel and other panels this week that we are moving in the direction of increased emphasis on the establishment and maintenance of normotension If this be the trend then it seems very likely that patients whose responsiveness to medical therapy is incomplete may be again suggested for surgical therapy I think this trend is likely to get an additional stimulus from the observations that the depressor effectiveness of sympathectomy is enhanced by chlorothiazide and certain of the other depressor agents I too feel that there is going to be an upswing in the number of patients suggested for surgical intervention

DR BOWER With the widespread availability of the antihypertensive drugs many patients are being treated for long periods before they are brought under observation and have well controlled drug treatment or surgical therapy This is a problem in medical education and it also brings into contrast again Dr Grimson's statement about the definite results of surgery and their irreversible state as far as the patient is concerned

DR SELLERS We are currently in the glorious phase of drug therapy with excellent responses Dr Smithwick has followed surgical patients for 15 to 20 years We don't know what kind of toxicity will be present when these drugs have been administered for that period of time I think there will still be a place for surgical treatment of hypertension

DR GRIMSON I think that the surgeons and the internists are in agreement on the patients who should be chosen for sympathectomy We agree that if a preliminary adequate trial of medical therapy is ineffective or has produced intolerable side effects or if the patient has been uncooperative or unwilling to follow the program it has been a failure These are the patients if they have severe hypertensive disease who should be considered for sympathectomy Certainly we wouldn't consider a patient in the latter category for adrenalectomy If the patient can't be counted on to take his antihypertensive medication how can he be counted on to take his replacement therapy after you have made him an adrenal cripple? I would personally choose medicine first and if I had to choose surgery I would prefer sympathectomy to adrenalectomy

DR ZINTEL I give adrenalectomy a slight advantage over sympathectomy because a greater percentage of adrenalectomy patients show more improvement in eyeground changes heart size EKG and so forth What the results will show in 15 years I don't know

DR BLAKEMORE It has been shown to us very clearly in this discussion that surgery can ameliorate this disease for the patient who is failing on antihypertensive drug therapy I think that there will be an increase in surgical patients in the future because with better education there will be fewer patients continued on antihypertensive drugs when the degree of hypertension correction is not enough to prevent deterioration of the vascu

lature to the brain heart and kidneys Many of our patients have failed on ganglionic blocking agents and have been satisfactorily treated by surgery

DR HOWARD Dr Grimson would you clarify a point? Most of the panel have said that they feel that medical failure is an indication for surgery and you state that those who do not respond to medical therapy would not respond to surgery

DR GRIMSON We ought to be thinking about full life expectancy to age 100 for people with hypertension Nothing less should be our objective We haven t reached it today Now if you re thinking about that we can take our grade III and do as I have treating five years with hexamethonium then with Apresoline and then adding to it the other agents If I then conclude that I should have done surgery five years previously and proceed with surgery the operation fails Let s decide in the beginning in progressive hypertension with a long term objective whether we are going to take this is a medical problem as a surgical problem or as a combined problem If we have a patient of 30 who is severely ill and has a bad family background and an elevated cholesterol and we re hitting for 100 I d say he ought to have the most extensive sympathectomy available and I m sorry I can t offer a more extensive one

DR HOWARD If I were to try to place this in perspective with what I ve heard throughout the week it would seem to me that the people treating hypertension are very much in the position of anesthesiologists There are a number of drugs that can achieve a purpose and frequently they are combining drugs and using two or three or four drugs This represents a phase It is probably less desirable to use several drugs simultaneously than to use one Drug therapy has replaced much of the surgery for essential hypertension Recently the exciting frontier of renal artery stenosis has opened up and we have no idea at this stage how widespread a cause of hypertension this is Another interesting concept that has come out has been Dr Smithwick s statement that his operation has been of less magnitude and that he has been combining operation with drug therapy reducing both the dosage of the drug and the magnitude of the operation Dr Grimson has stated that long term medical failures are not good candidates for sympathectomy We have watched the pendulum swing down with Dr Smithwick s curve of incidence of operation Having reached the low point in the swing we again are beginning to take stock The role of the surgeon is not a role of the past

B THE EFFECT OF THERAPY ON PROGNOSIS IN PATIENTS WITH HYPERTENSION

PANEL DISCUSSION

CHARLES C WOLFERTH SR *Moderator*

A C CORCORAN	JOSEPH IMBRIGLIA
WILLIAM DAESCHNER	WALTER KIRKENDALL
FRANK FINNERTY	WILLIAM LIKOFF
EDWARD FREIS	MARVIN MOSER
ARTHUR GROLLMAN	HENRY SCHROEDER
SIBLEY HOOBLER	ALFRED SELLERS

REGINALD SMITHWICK

DR WOLFERTH We are now to discuss what is probably the cornerstone of clinical knowledge namely prognosis because in order to discuss any new therapy successfully you must know what happens to the patient who does not get treated or to the patient who gets conventional treatment This must then be compared with the prognosis in the patient who gets the type of treatment that you are advocating at the time Perhaps the first thing we ought to discuss is the question of what people with hypertension die of I do not mean to imply that prolongation of a miserable existence is necessarily the goal of treatment of hypertension The goal of treatment is the maintenance of an individual in a reasonably happy state and I mean this in the sense in which it is ordinarily used that is an individual leading a useful life reasonably free from too much handicap and discomfort I think increased duration of life under those circumstances is perhaps the goal of treatment of hypertension as well as many other things

We can perhaps approach this first by trying to find out what people die of Dr Imbriglia you are the pathologist and doubtless have some ideas as to what hypertensives are apt to die of

DR IMBRIGLIA Most of us agree that hypertension is a generalized vascular disease However the effects and the changes in certain viscera of the body are more apparent than in others There are changes in the pancreas the adrenal glands the intestinal tract the spleen and other organs but patients die from (1) the effects on the heart which include coronary artery disease and occlusion and chronic congestive heart failure or (2) a certain per centage die as a result of changes (probably the most spectacular lesions)

in the kidney which lead to uremia and (3) another certain percentage will die of cerebrovascular accidents incident to the changes in the vessels in the brain

Dr Schroeder I think it ought to be pointed out that a fair number of hypertensives die of something other than hypertensive vascular disease In all series that have been studied there is a moderate percentage of them that die of cancer automobile accidents or degenerative diseases

Dr Wolferth Sometimes Dr Schroeder at the age of 80

Dr Schroeder Some 30 per cent of the older hypertensives who get their hypertension late in life die of nonhypertensive and nonvascular diseases In other words they go along and live out their life expectancy to be 80 if they do not get cancer or other unrelated diseases in the meantime

Dr Smithwick The figures that I have in mind for people who develop hypertension below the age of 50 show that about 60 per cent die of cardiac complications 25 per cent from cerebral causes 10 per cent from renal causes and 5 per cent from other causes These are for the essential hyper tensive patients

Dr Corcoran That is before the availability of effective methods of treat ment I have not seen a cardiac death from heart failure for some years

Dr Smithwick I am thinking in terms of what little we know of the so called natural history of the disease

Dr Corcoran We followed a group of severe hypertensives who had been treated for five to six years and we tried to determine the various causes of death These people had all received one or a combination of various drugs The survival rate in this group at the end of six years was in the order of 30 per cent

Dr Wolferth What happened to the rest?

Dr Corcoran A considerable fraction came to us particularly in 1951 1952 and 1953 with advanced renal disease and in spite of treatment died of renal failure within the first few weeks or months of observation This accounted for 20 per cent of the deaths The remainder who died in this interval died largely of causes which we could think of as atherosclerotic Some died of myocardial infarcts which in the untreated malignant hyper tensives are relatively uncommon Two patients died from rupture of aortic aneurysms even in spite of good blood pressure control Cerebral thrombosis and cerebral hemorrhage were observed frequently Cerebral hemorrhage was associated in general with inadequate control of blood pressure whereas the mild myocardial infarcts and the aortic disease were not associated with inadequate control of blood pressure but with very severe pre existing malig nant hypertensive disease We view these as late consequences of the injury done to the large vessels during the period of malignant hypertension Par ticularly interesting was the phenomenon that we labeled "delayed renal failure" people who after one to four years of pretty well sustained renal

function perhaps at 30 per cent or 40 per cent of normal began slowly to go into renal failure and died in uremia Autopsies showed a diffuse fibrous hyperplasia not of the small renal arterioles and small renal arteries which are the sites of predominant damage in the acute phase of malignant hyper tension but in the large arcuate interlobar and interlobular arteries A similar phenomenon we believe has been reproduced to some extent in the rat made hypertensive and in which the hypertension is partially controlled with Apresoline This too we view as a postmalignant hypertensive atherosclerotic phenomenon conditioned by the pre existing disease and allowed to assume this new manifestation because life is prolonged by the period of antihypertensive treatment In summary, the patients either died of early renal failure because they received treatment late in the course of the disease or they died of atherosclerotic disease that is cerebral cardiac aortic or renal or they survived more than six years and I suppose still have an increased incidence of atherosclerotic damage

Dr Wolferth Dr Smithwick your group of patients that you have operated on is to a certain extent a selected group I read your paper very carefully on the matter and I hesitate to ever ask a surgeon whether any of his patients died but if any of them did die what kind of things did they die of? We did not hear very much about cardiac failure from Dr Corcoran You didn t mention cardiac failure as being very common

Dr Corcoran We have not seen cardiac failure as a primary cause of death in hypertensive patients for some years since the use of ganglionic blocking agents

Dr Freis Our experience is quite similar to Dr Corcoran s except that our five year survival is not as good as his in the malignant hypertensive group and our primary cause of death is a gradually developing renal failure The second most common cause of death is cerebral hemorrhage Arteriosclerotic complications make up the remainder Congestive heart failure is strikingly absent as a cause of death

Dr Corcoran May I ask whether the patients with slowly progressing renal failure show primarily a large vessel disease with the small vessels showing healing or a healed status?

Dr Freis Yes at autopsy they show benign atherosclerosis rather than malignant atherosclerosis

Dr Wolferth In the past many hypertensive patients died in the state of cardiac failure and we felt that cardiac failure was the most important cause of death prior to the advent of effective antihypertensive drugs Now to get back to Dr Smithwick your patients are selected They are a little different from this group but aside from those who died from being run over by an automobile what were the causes of death particularly in the treated group?

Dr Smithwick Among the patients who have been operated on the principal change has been a rather noticeable decrease in cardiac deaths by comparison with the figures that I just quoted for untreated patients

The situation in regard to cardiac and cerebral deaths is approximately reversed That is the cerebral deaths are much more common than the cardiac deaths Renal deaths are more or less status quo

DR. WOLFERTH Now Dr Sellers the group of patients with the combination of adrenalectomy plus sympathectomy is a much smaller group of course but what has been your impression of the causes of death in this group of patients?

DR SELLERS We too have noted a change in the spread of the causes of death among these patients as compared to what one used to read in the older textbooks We have not had a single death due to congestive heart failure Another striking factor has been the apparent increase in the number of deaths caused by cerebral vascular accidents coronary occlusion is a lesser cause of death even less frequent than uremia This has been in association with remarkable preservation of renal function in patients operated on with adrenalectomy

DR WOLFERTH Dr Kirkendall you gave a paper on what happens to the eyegrounds How would that bear on the problem of hypertension? I think that this is a very significant thing because there are small blood vessels in there that you can take a look at and see pretty much what is going on

DR KIRKENDALL I think that the retina is an excellent vantage point Our findings which are really short term results show arteriosclerosis advancing as therapy is continued This is the point which seems to be a little bit different from the observations of Dr Corcoran That is in his patients who died of renal failure there was advancing larger artery disease but not much in the way of arteriolar sclerosis I suspect that this discrepancy may be due to the short term nature of our study Our patients have been followed for only a year and very likely the arteriolar process may level out as time goes on and be less of a problem Nevertheless as far as the process is concerned in general if one lowers the blood pressure I think you can say unequivocally that the angiospastic and hypertensive changes in the ocular fundi will disappear with very rare exceptions There is the unusual individual whose eyegrounds do not clear up very well with blood pressure control But in general the hypertensive and angiospastic changes clear very rapidly with good control of blood pressure The other changes I think are more of a mystery to us right now They are certainly a challenge if they do persist in progressing

DR WOLFERTH Was there any specific type of treatment that you felt produced this lessening of angiospasm in life?

DR KIRKENDALL We did not study that particular point because as a matter of fact we do not know what our patients are on right now We correlated this only with the blood pressure changes and the eyeground changes We have not correlated it with the type of therapy It is simply whether their blood pressure dropped or not

DR WOLFERTH Dr Schroeder you are one of the pioneers in the use of antihypertensive agents What do you think they do to this disease hypertension?

DR SCHROEDER If I can talk about combination therapy of heavily treated patients since all of our patients are heavily treated with a relatively high dose level of ganglionic blocking agents and hydralazine I think there is no question at all that the life expectancy improves if one studies the worst cases It has been of great interest to us to find azotemic patients living for four to five years Now usually it is considered that when azotemia has developed in this disease prognosis is a matter of months We have seen gradually developing azotemia during treatment and azotemia that was present before treatment slowly getting worse We have also seen it become stationary and occasionally we have seen it regress as long as the blood pressure was kept normal Recently Dr Perry and I compared our group of drug treated patients selected only in that they were grade III and grade IV using Dr Smithwick s criteria I must say that the two groups were not exactly comparable because I have the impression from reading Dr Smithwicks criteria that ours were worse as far as renal disease was concerned in that only six of our 80 odd patients were able to excrete more than 15 per cent of PSP in fifteen minutes none of them excreted more than 22 per cent and the rest excreted less than 15 per cent Dr Smithwicks patients were cooperative after they had a sympathectomy obviously they cannot grow their nerves back voluntarily If we took our cooperative and uncooperative patients together we had about the same mortality as Dr Smithwick had If we took our cooperative patients those we were able to convince should stay on the drugs and keep their blood pressures at normal levels or close to normal levels we did about twice as well as he did with similar grade III and grade IV patients

DR WOLFERTH How many patients have lost their vascular reactivity or whatever you choose to call it?

DR SCHROEDER We have something over 30 now out of several hundred patients who have been able to reduce their dose of both drugs to a minimum or omit the drug almost entirely and still remain normotensive I say omitted *almost* entirely For example some patients will take 25 mg of hydralazine every other day or perhaps once a week or ¼ mg of reserpine three or four times a week which is almost tantamount to complete removal of the drug We have had some who have been able to get off drugs and then continue of course taking their blood pressures at home Many of these remained normotensive for a few months and then hypertension returned They have gone back on small doses and the hypertension has disappeared that has happened in several instances We cannot help but feel that there is some change in the direction away from the hypertensive process that is some reversal of the process in some patients I think Dr Corcoran has gotten some autopsies and renal plasma flows on patients of that sort to bear this out There is some healing that goes on with time

DR WOLFERTH Dr Corcoran I wish you would comment on that very interesting group of patients with very bad kidneys that you reported

DR. CORCORAN In accordance with Dr Schroeder s report our experience has been that azotemia *per se* is not a contraindication to treatment I do not know how you define azotemia Your definition of the untreatable azo

temia Dr Freis was a BUN of 70 mg per cent or higher I think I tend to agree with you that somewhere in the range between what is normal and 70 mg per cent there are people who are desperately ill whose course has been rather rapid and severe who show some very definite signs of severe renal disease and who appropriately treated may show a considerable regression This is noted not only in the signs of active nephrosclerosis but also in an increase in phenol red excretion and in PAH clearance I can recall two patients in particular both women who had renal blood flows on the order of 200 cc or so per minute in whom renal blood flow over a course of two to three years rose to levels of 450 or thereabouts Both patients died of cerebral vascular accidents during the third to fifth year of treatment Autopsy showed excellent healing of the lesions of malignant atherosclerosis the residual being benign sclerosis

Dr Schroeder The patients whose diastolic pressures have not been normal have never in our experience been able to reduce the dose of their drug We titrate their drug dosage against this pressure It is an interesting thing that those patients who kept their diastolic pressures below 90 or at least below 100 in the three year period can take much less drug now but the patients whose diastolic pressures ranged from 100 to 115 on the average cannot reduce the dose of their drug and there are no signs that a reversal has occurred We think that they are still hypertensives although modified considerably from the original

Dr Finnerty We have followed 13 patients who would fall into such a group that is patients showing diastolic pressures of 140 to 150 mm Hg with overwhelming vasospasm flame shaped hemorrhages in the retina and papilledema When they were treated with ganglionic blocking agents or some other regimen for several weeks they got reversal of the malignant phase to the stage that we have reduced our therapy to reserpine alone in some patients we took the reserpine away entirely and these patients have done extremely well for an additional six months Then the blood pressure came back up again vasospasm returned and flame shaped hemorrhages developed in the retina It is significant I think that in these patients there were no obvious signs of sclerosis If you looked at their fundi you would not see arteriovenous nicking etc but you would see the vasospastic phenomenon It is of further significance that in nine of these 13 patients renal biopsy revealed glomerular disease So it seems that this would agree with what has been said here previously that lowering blood pressure certainly would reduce the complications of the elevated blood pressure itself but does not change the state of the sclerosis

Dr Wolferth I would like to ask Dr Grollman a question I think that we all agree that the classification of patients into grades of severity of hypertension such as Dr Smithwick has done has undoubtedly been a very valuable aid in prognosis Dr Grollman was moderator of a program in which basic concepts of the etiology of hypertension were discussed Dr Grollman it would be a great help in the prognosis of hypertensive disease if we could split this large group of patients with hypertension into some of the etiologic types that were discussed How far can we go along those lines in the classification of these patients that would be helpful to us in prognosis?

DR GROLLMAN I think we can go rather far Dr Wolferth depending upon what our concepts are regarding the pathogenesis of the disease In the first place when we have an obvious origin as in chronic glomerulo nephritis we must obviously consider the effect of that disturbance There are certainly many patients with glomerulonephritis or with diseases of the vascular system affecting the kidney who die ultimately from their primary disease rather than from the hypertension Then of course we have a group of hypertensives in whom there is apparently a different pathogenesis than in the case of essential hypertension In those with unilateral renal disease with a plaque in the renal artery or in those having hypertension secondary to hyperaldosteronism we can produce almost a curative effect on the blood pressure But even here we have a certain proportion of failures which are attributed either to the induction of irreversible hypertension or to the fact that these findings happen to be incidental Since hypertension is so common you would expect to find a certain group of hypertensives who happen to be harboring either a nonfunctional paraganglioma or a chromo phil cell tumor

It is in the large group of hypertensives meaning the essential hyper tensives that the argument regarding pathogenesis is most argued I say here even the most optimistic therapist medical or surgical would have to admit that our present methods of treatment are nonspecific in the sense that they do not overcome the basic defect in the disease Hypertension of the essential type is a systemic disease in which the elevation of blood pressure represents simply a hemodynamic manifestation In all available methods of treatment we are getting rid of this manifestation which we will also have to admit is an injurious one insofar as the body is concerned For example it puts a great mechanical strain upon the heart and that is the reason for the beneficial response to treatment by blood pressure reduc tion In other words presently available methods of therapy will only ameliorate the disease and arrest that part of the disease due to the elevation of pressure *per se* We admit that this is the case and by getting rid of this one function only we prolong the life of the patient

DR WOLFERTH Dr Likoff I have been impressed for a long time with the effects of myocardial infarction on hypertension A lot of people who have hypertension and get an infarct have a fall in blood pressure and it may be very slow in going back up again In fact it may never go back to the levels that existed prior to the occurrence of the infarct I would like to know if this is purely a hemodynamic effect I used to tell my students long ago before we had all of these modern methods of treatment that I thought a good myocardial infarct was the most effective way of treating severe hypertension

DR LIKOFF As already implied in the previous discussion the avenues of effect upon the heart itself from hypertension are basically two (1) that which is exercised through the increase of peripheral vascular resistance and the hemodynamic effect that Dr Wolferth has already referred to and (2) that which occurs as a result of a basic compensatory mechanism that is myocardial hypertrophy When either of these two effects is exercised in the heart pathophysiologic alterations develop as you know In reference to whether or not there is a beneficial response in having a low blood

pressure following an extensive myocardial infarction one can only reason that one of the mechanisms responsible for producing a symptom of this disease namely high blood pressure has been removed and that forceful systolic injection is so badly interfered with that the blood pressure no longer is elevated I think in either case this is not an indication that the disease from a systemic standpoint has been improved In that sense I do disagree with the basic concept that a lower blood pressure following myocardial infarction is beneficial It is true however and this is a peculiar fact and is paradoxical to the basic statement I made that it does appear to me clinically that those patients whose blood pressure is lowered by the action of a significant myocardial infarction somehow or other seem to do better and have fewer complications and a better prognosis

Dr Freis I agree that some of the methods used for reducing blood pressure are not physiologic in the sense that they do not reverse the specific abnormality that we recognize in hypertension But regardless of whatever method you use to reduce the blood pressure you seem to do something to the organism to make it readjust and to readjust at a lower level of pressure and this is the thing that seems to be beneficial

Dr Corcoran I would view this phenomenon as part of the concept I was trying to formulate before as part of the homeostasis of blood pressure that is practically anything you do even at the cost of a considerable physiologic abnormality which restores pressure to normal for some significant time results in a new level which tends to some degree to be self sustaining in a considerable proportion of people particularly those with rather acute disease I remember a patient with malignant hypertension whom we had in Indianapolis and who was treated with kidney extracts and who had pyrogenic reactions during the course of which he had a myocardial infarction He never had any hypertension again He lived for eight years and died of progressive arterial sclerosis He had no further antihypertensive medication after that one infarct but he had a rather acute process dramatically reversed I think he reset his blood pressure controls

Dr Likoff Did I understand that to be in a case with malignant hypertension or one with essential hypertension?

Dr Corcoran This was a patient who had retinopathy and all of the rest of the malignant syndrome including renal disease

Dr Finnerty This is a fairly common affair after myocardial infarction and it is also a nonspecific effect of surgery Those of you who have seen middle aged people go to surgery for removal of the gallbladder or appendix have observed that they often remain normotensive for six months following surgery Indeed I would think that some of Dr Smithwick s patients show apparently short term good results not due to the cutting of the sympathetic nerves but just as a nonspecific effect of surgery

In a patient with a lot of vasospasm if you can suddenly reduce the blood pressure regardless of the way you do it you will frequently find a low blood pressure long beyond the effect of the procedure that is six or seven days following a short acting drug What this means I certainly do not know

but it goes along with Dr Corcoran's theory that if you have normotension it begets normotension

Dr Corcoran I think you're waving the flag of Ireland in the direction of Dr Smithwick

Dr Wolferth Before Dr Smithwick speaks I think I should remove any impression that anyone may have that I have been advocating myocardial infarction in the treatment of hypertension I merely brought it up as an interesting point for discussion

Dr Smithwick I was interested that Dr Finnerty put in the time limit of six months which I think is important A number of articles were written some 20 years or so ago about the nonspecific effects of operations of one sort or another that is cholecystectomies hysterectomies and what not These patients were all followed for very short periods of time So at the time when Dr White and I were struggling with this problem we looked up a large series of patients who had had nonspecific operations We could not find any in which there was any evidence that the hypotensive effect lasted even as long as a year That is one reason why I have never reported the results as far as blood pressure is concerned unless the patient was followed at least one year I think that this is probably a reasonable length of time to eliminate nonspecific effects

Dr Wolferth I asked Dr Smithwick a question up here before the panel began Why does chlorothiazide have such an amazing effect on the residual hypertension of patients who have had sympathectomy? Would you like to talk about that Dr Smithwick?

Dr Smithwick I am sure that I do not know why it is I suppose it has something to do with sodium metabolism one way or another We have not done any detailed physiologic studies with that group of patients Just on clinical grounds over the years we have been tremendously impressed by *how much more sensitive a sympathectomized patient is to low sodium diets* This is so whether it be the rice diet or whether it be a diet of the type that Dr Grollman described many years ago We find patients who will not respond to sodium restriction but who after operation will I have automatically thought in those terms in regard to chlorothiazide because that does seem to be its most striking effect That is it enables the patient to eat salt and not retain it Somehow or other I presume this is the physiologic mechanism involved

Dr Wolferth Dr Grollman would you agree with Dr Smithwick or do you think that there is something else to it?

Dr Grollman In a normal person with an intact sympathetic nervous system any tendency for the blood pressure to drop will be prevented by the homeostatic mechanism maintained by the sympathetics Therefore when you combine two procedures whether it be sympathectomy and a drug or two drugs the combination will always work better because it prevents the homeostatic reaction

Dr Wolferth It seems to me from my limited observation that this is

a very amazing effect I just wonder if I could get some more hypotheses from Dr Freis?

DR FREIS I think part of the answer lies in the plasma volume depletion produced by chlorothiazide In an individual whose sympathetic vasoconstrictor nerves have been cut removal of blood either by venesection or reduction of plasma volume by chlorothiazide results in reduction of blood pressure that you would not see in the person who has compensatory vasoconstriction I don t know whether that is the whole story or not but I think it is a very important element in this increased sensitivity

DR CORCORAN Dr Dustan and our group have gathered evidence as others have that chlorothiazide depletes plasma volume During this depletion of plasma volume vasomotor tone is intensified and of course the sympathectomized person cannot enhance his vasomotor tone comparably to the normal person consequently he cannot maintain his blood pressure nearly as well

DR WOLFERTH Dr Daeschner?

DR DAESCHNER You have been talking about an area that I have not had any experience in but I do have a comment to make concerning the treatment of chronic hypertension associated with chronic renal disease The first patient is an example taken from several similar cases This child is nine years old at this time We started seeing him at the age of five when he was comatose Treatment was more successful than we had anticipated Now four years later the blood pressure has been maintained on much reduced doses of drugs He is back in school in the third grade and is normal and is doing quite well Over a period of 38 months we have had the opportunity to study his renal function Although the blood pressure has remained down the renal plasma flow and the glomerular filtration rate have remained approximately the same I think that while this child has not been cured of his renal disease the progression of it which we would have anticipated without treatment has not occurred Three and one half years later he is a healthy active boy who has not experienced any mental depression from reserpine and he is attending school regularly His height growth and weight growth have not been perfect and I suspect that his prognosis remains quite guarded but at least he has had 3½ years—probably one or two more than he would have had without treatment

DR WOLFERTH Dr Sellers I know that you have been interested in the effects of chlorothiazide in hypertensives who have not been subjected to surgery in patients with sympathectomies of the type that Dr Smithwick has done and in patients with the combination of adrenalectomy and sympathectomy I wonder what you might have to say about these

DR SELLERS I think there can be no question about the effectiveness of chlorothiazide and what it has done to medical and surgical treatment as we look at it today The number of patients who currently present themselves for surgical treatment has greatly diminished because of the over all effectiveness of the drug We originally gave chlorothiazide to 70 patients most of whom had been refractory to hydralazine ganglionic blockers or Rauwolfia drugs Sixty five of these 70 refractory patients who had been

unresponsive did have a fall of at least 20 mm Hg mean arterial blood pressure following addition of chlorothiazide The remarkable changes that occur with chlorothiazide after sympathectomy or adrenalectomy originally impressed us and resulted in our trying to get back to the hospital as many as possible of previous operative failures because the fall in blood pressure in these patients is very dramatic when chlorothiazide is given One of the first things that we have seen in the previously sympathectomized patients is the return of their postural hypotension even though they might have been operated on eight nine or ten years previously It is also amazing that one can give doses as large as 500 mg of chlorothiazide to people who have had total adrenalectomy without precipitating adrenal insufficiency These are patients who obviously are getting normal amounts of replacement therapy Why the drug is so remarkable in its effect in these patients I dont know Along with what Dr Grollman said I think that it is worth pointing out that chlorothiazide is effective in these patients without the addition of Rauwolfia or hydralazine or other agents It may be as Dr Grollman implied that the sympathectomy or adrenalectomy is taking the place of the second agent In other words the chlorothiazide is potentiating the operative effect rather than potentiating the medical sympathectomy of ganglionic blocking drugs

Dr Schroeder I dont think this applies specifically to chlorothiazide It applies to any combination of drugs or procedures The sympathectomized patient is more sensitive to Apresoline than the nonsympathectomized patient The sympathectomized patient is more sensitive to many other procedures such as ganglionic blockade If we look at the things that raise blood pressure experimentally we have three types of procedures One has to do with the adrenal steroids or salt another has to do with the nerves and another one has to do with the kidney We have at least two drugs that seem to act on two of those natriuretics and sympathetic depressive drugs The third hydralazine I suspect we will find some day is a direct smooth muscle relaxor and may destroy the humoral pressor substance It certainly does it *in vitro* So any combination of drugs acting on different aspects of the human dynamic picture do better than any one Any three do better than any two It does not matter whether it is salt restriction and sympathectomy or Apresoline and sympathectomy or ganglionic blockade and so forth

Dr Kirkendall We know that a person with elevated blood pressure has more chance of dying of vascular disease than his counterpart who has normotension What I would like to know is how does therapy influence the death rate of Smithwick group I or II patients? It has been said many times that it is going to take 15 or 20 years of observation to be sure about this and I quite agree But Dr Smithwick has a group of patients now that he has called his controls and I wonder if he has been able to keep enough of those out of the hands of internists and their drugs to make any observations other than the ones he has made in the past on these particularly interesting groups

Dr Smithwick I think if a physician is really interested in having his patients live to anywhere near a normal life expectancy that the earlier treatment is instituted whatever it may be the better

C SUMMARY TODAY'S RECOMMENDATIONS FOR DRUG THERAPY OF HYPERTENSION

PANEL DISCUSSION

JOHN H MOYER *Moderator*

A C CORCORAN	WILLIAM HOLLANDER
WILLIAM DAESCHNER	JOHN HOWARD
JAMES DONALDSON	EDWARD MEILMAN
FRANK FINNERTY	MARVIN MOSER
RALPH FORD	WILLIAM PATON
EDWARD FREIS	H MITCHELL PERRY
RAY GIFFORD	HENRY SCHROEDER
ARTHUR GROLLMAN	REGINALD SMITHWICK

DR MOYER As you know the panel today is a working panel The panelists are from different areas of the country Many have different ideas as to how to treat hypertension We hope that the ideas are representative of the various geographical areas First we will discuss the treatment of the ambulatory patient with hypertension and then the treatment of hypertensive emergencies

TREATMENT OF THE AMBULATORY PATIENT

Before we discuss specific therapeutic approaches we ought to decide just what is to be treated I would like to ask Dr Perry if he will tell us exactly what he considers treatable hypertension In other words when a patient comes into your office just how severe must the hypertensive disease be before you think he deserves specific therapy?

DR PERRY I think this depends on what kind of treatment you are talking about In general the kind of treatment that I feel I can talk about unequivocally is pretty potent treatment and this is treatment I would advise for someone who I think is going to get into trouble from his hypertension in the foreseeable future In general this would be the kind of patient who within a period of a couple of years might expect to develop a complication such as cardiac failure

DR MOYER Is this the only type of patient that you would treat? We are interested right now in the borderline case so as to define the lower limit of hypertension that should be treated or shall we say the upper limit of

normal After we have decided this then we can go on to devise methods of therapy

DR PERRY No this is not the only kind of patient I would treat but this is the only kind of patient about whom I can really feel completely assured in my own mind that we have data indicating that we will help The other people I honestly believe we do help but I think that we have to keep in mind that we don t have the data which support the thesis that blood pressure reduction really does help them

DR MOSER We should treat every single hypertensive patient by doing something and doing something may mean just using sedation or psychotherapy Treatment means beginning the patient on a regimen whether it is advising the patient to take it a little bit easy decrease his salt intake or lose weight I think we should make that fairly clear Dr Perry is talking about treatment with specific antihypertensive drugs that are potentially dangerous or perhaps carry some risk to the patient What we are trying to get at here is that before we use a drug with even a minimal risk it should be justified on the basis of improved prognosis and knowledge of the natural history of the disease

DR CORCORAN We have been discussing things largely in terms of the empirical When do you treat? On the basis of what time in the natural history of the disease do you start therapy? I wonder if the panel can perhaps take a philosophical position We should have the concept of a certain homeostasis of hypertension Yesterday it was stated that hypertension tends to beget hypertension and that hypertension can be self sustaining For example as Dr McCubbin has shown in the dog when renal hypertension is produced after some time there is a shift in homeostasis so that that hypertension which was initially renal and possibly renal humoral in origin in some way becomes in effect neurogenic We have seen other examples of this tendency of hypertension which was prolonged to become self sustaining Now if one sees that this is a fact then it would follow that relatively mild hypertension deserves some form of management that is it deserves whatever is required to restore blood pressure to normal for a prolonged period If there is a homeostasis of hypertension there is also homeostasis of normotension and if we can restore pressures for long periods to normal they do sometimes tend to remain there We see that particularly in children with what seems to be essential hypertension In hypertension of brief duration vigorous treatment with antihypertensive drugs restores blood pressure to normal and after a while the drugs can be discontinued So if hypertension is a reversible process and if once reversed the blood pressure does tend to self sustain its normotensive levels I think that there is every indication for whatever is required to restore blood pressure to or toward normal even if there is some small risk involved Really the risks involved with some of the present day medications are relatively easy to avoid if the patient is reasonably well followed

DR MOYER Then you are also implying that hypertension associated with progressive vascular degeneration originally comes from the milder case of hypertension and that for that reason even the patients with mild hypertension are deserving of therapy?

DR CORCORAN Yes Patients with progressively more severe hypertension commonly develop a premature atherosclerosis of the coronary cerebral and other vessels This accelerated arteriosclerotic process is possibly also a function of the mild hypertension and is I suppose remediable by control of the blood pressure Certainly there is experimental evidence for this conclusion

The evidence for the benefits of improved prognosis in severe hypertension has been reviewed Dr Schroeder said the other day that even though we don t have evidence at hand now which would validate the concept mild hypertension should be rigorously treated or managed in whatever way is necessary to effect the desired result But we have some evidence accumulating at least in those you would classify as grade II and III hypertensives indicating that life expectancy is increased in various ways There is evidence accumulating that in hypertension of short duration treatment can result in self sustained normotension after a while

DR MOYER Any serious objections to this concept?

DR FREIS There are a number of mild hypertensives that I don t treat with specific drugs which lower blood pressure because I think they are neither safe enough nor cheap enough to warrant their use There are certain criteria which you can use to help you in this although it is a very difficult problem to decide which patient has the kind of hypertension that will get him into trouble and which does not But I would suggest a few things

One thing to consider is the age of the patient The older the patient the less inclined I would be to treat him and if he were over 70 I wouldn t treat him unless he had severe hypertension

The sex of the patient is another consideration I am thinking particularly of the middle aged menopausal female who has high blood pressure under stress but in whom the home pressures are normal or the hospital pressures are normal However some of these patients who seem very labile really do have hypertension even at home and it is very difficult to tell by looking at the patient But there are a few other things that a doctor can do He can look in the fundi and see vascular changes spasm and so forth He can see by x ray whether there is any cardiomegaly and by electrocardiography whether there is any change in the electrocardiogram A urinalysis will detect whether or not there is any albuminuria Abnormalities in any of these observations indicate hypertension that is deserving of antihypertensive drugs When this type of middle aged female patient is referred to me I try to get some home blood pressure recordings for a couple weeks This helps me a great deal in making the decision as to whether I should treat with drugs

I think there are two sins One is the sin of omission when you don t treat intensively enough but just give drugs without any specific purpose of lowering blood pressure in the patient who *should* have his blood pressure lowered the other sin is to overtreat a patient who shouldn t have treatment except for mild sedation and psychotherapy

DR MOYER Do you say this despite Dr Corcoran s comments about every patient deserving therapy even if he has mild and labile hypertension?

DR FREIS Yes I say that because of the present stage of development of our chemotherapy Our chemotherapy is far better than it was five years ago But it is not perfect yet If we had a pill that was absolutely safe that was inexpensive and that would uniformly control the blood pressure at normotensive levels with one dose of the drug each day then I would say by all means treat all hypertensives But since we haven t reached that stage we still have to be selective

DR MOYER You are speaking about specific antihypertensive therapy which probably depresses the autonomic nervous system?

DR FREIS Yes that is true I was referring to specific antihypertensive drug therapy As Dr Moser indicated you treat every patient who walks into your office even if all you do is talk to him and follow him along for observation That is a form of treatment also

DR MOYER I might ask Dr Smithwick whether he will agree with what Dr Corcoran has just said that more severe hypertension which is associated with vascular degenerative changes arises from a group of patients who at one time had a milder type of disease and that specific therapy is indicated in this milder group of hypertensives

DR SMITHWICK I certainly would agree with that in general The disease evolves through stages What people die of are the cardiovascular changes In general as Dr Freis says if you ever get a pill that is absolutely safe and that you can give in the stage of intermittent hypertension before the blood pressure is continually elevated then I would think you have the best chance of preventing this disease from ever developing into anything bad I would favor that conclusion

DR MOYER There was some mention yesterday about treating numbers and I believe there was some objection raised I am referring to the use of manometric blood pressure observations as a guide to therapy This objection seems quite inconsistent with the practices of practically all of the panelists here because I notice that despite the fact that we say we should not treat numbers (that is use manometric observation as a guide to therapy) we practically all do This then makes us come around to a consideration of what the diastolic level of blood pressure is before drug therapy is indicated May I ask Dr Ford specifically what the numbers are that he treats relative to diastolic hypertension?

DR FORD I m not sure that I understand the type of patient that Dr Freis would not treat Anybody regardless of age who makes three visits to the office or clinic for recording of blood pressure and two out of three times the blood pressure is greater than 155/95 gets treatment

DR MOYER This is even without evidence of vascular changes other than arteriosclerotic changes?

DR FORD This is numbers—155/95 and two out of three visits

DR MEILMAN I think this discussion points up the great need for common

definition and agreement Frequently someone makes a comment that he has picked arbitrarily one level of blood pressure maybe 140/90 or 160/100 Until we get some agreement as to what we are talking about I dont see how we can compare treatment programs of any kind

Everyone seems to be agreed that we treat the patient with evidence of the degenerative disease either the heart has gotten into trouble or there is some kidney damage We all agree that we are going to treat the fellow who is already in trouble If normotension begets normotension maybe it is easier to treat the patient when the disease is milder before there is overt evidence of advanced vascular damage I realize too that we havent got the ideal drug but I agree with Dr Ford that we should treat the patient with a mild increased diastolic pressure even before there is clinical evidence of vascular damage which obviously is an advanced stage of the disease

DR MOYER Dr Meilman you refer to mild hypertension which is an ambiguous term

DR MEILMAN Yes As I pointed out we have to make definitions first

DR MOYER What is mild and what is severe hypertension and what is the diastolic pressure that is considered abnormal? We are here to define

DR MEILMAN Well if we are going to start with the numbers I think that the numbers have been castigated too much in recent years I often wonder how you would take care of the patient if no one had invented the sphygmomanometer You would have a terrible time taking care of such a patient You wouldnt treat any patients until they were in serious trouble

DR MOYER May I ask what this number is then?

DR MEILMAN I can give you *my* number 150/100 happens to be my number Any patient with blood pressure above this receives antihypertensive drugs

DR FINNERTY When I was in the service I happened to be stationed at the Pentagon which is really a nervous in the service" institution and the numbers were ridiculous—220/130—numbers in somebody who in a couple of days would come down to a not so ridiculous number I have also noted that if a person was sensitized to the home blood pressure recording the more he took his pressure the more this patient was sensitized to the noxious stimuli of the blood pressure being taken With a certain group of patients the physician would be much more intelligent if he threw the blood pressure cuff away I found it very useful to divide patients with hypertension into those with vascular disease and those without vascular disease and didnt consider the arterial pressure as a manifestation of vascular disease but considered the objective findings only that is vascular changes in the eyes heart kidneys and so on

DR MOYER Then you are going to be satisfied with treating only advanced hypertensive vascular disease as Dr Meilman has just pointed out Of necessity vascular damage has to be far advanced before we can discover it

clinically with the crude diagnostic tools available to us After all when cardiomegaly can be determined clinically this disease is well advanced Even the electrocardiogram is not so good for this purpose since many a patient has died of a coronary occlusion at a time when his electrocardiogram was entirely normal Autopsy frequently confirms advanced coronary artery disease under these circumstances

DR CORCORAN As Dr Moyer indicates the patient might have vascular disease that you can t see so you can t really make the diagnosis of hypertension with no vascular disease

DR FINNERTY I mean vascular disease that can be seen

DR CORCORAN And too you speak of a group of people who are sensitized to home blood pressures (most of our patients are taking their pressures at home or are having them taken) I think there were about three people I can think of out of the whole group who became sensitized One was very seriously sensitized But that is an exception in our experience

DR FREIS I agree with Dr Corcoran about the home blood pressure recordings You can usually spot the patients who will react adversely They are unreasonably and irrationally fearful about almost everything and that type of individual should not be given a blood pressure cuff

DR MOYER Dr Finnerty apparently is a strong advocate of stress being a motivating force in hypertensive vascular disease As you remember many members of the panel disagreed with this concept

Dr Finnerty you bring up a question which the panel more or less agreed upon and this is that patients with labile hypertension apparently serve as the pool for patients who will develop more severe and progressive disease and for that reason we have decided that a therapeutic approach should probably be undertaken in such patients We have agreed that many of these patients have hypertensive disease and that the disease is likely to progress Therefore we have to decide what level of blood pressure constitutes hypertension which is severe enough to warrant therapy Dr Smithwick would you care to express an opinion on this?

DR SMITHWICK The important consideration is the manner in which the patient s cardiovascular system reacts to whatever degree of hypertension he may have You never discuss this subject anywhere without somebody getting up in the back row and saying I ve got a patient who has had a blood pressure of 300/200 for fifty years Of course that is the exception and when you pin the gentleman down you always find he is talking about a female rather than a male Of course I think that is an important consideration There is a tremendous difference in the capacity of the female to tolerate the same degree of hypertension in comparison with the male

We all should agree on the minimal cardiovascular data you ought to get on a patient before you treat him and then consider the question of how that patient is tolerating what degree of hypertension he has I find from my own experience that one thing doctors never do is to find out anything about the kidney I think this is terribly important The most valuable simple really

good test of renal function is the intravenous PSP test with reference to the first 15 minute output Every patient ought to have that I think they all ought to have an electrocardiogram You can evaluate heart size on a clinical basis All patients ought to have their eyegrounds examined I think that if a person has normal eyegrounds a normal electrocardiogram a PSP output of 25 per cent or more in 15 minutes and a negative urine and clinically his heart is all right you are reasonably secure in saying that the patient does not as yet have serious cardiovascular changes of consequence as a result of the hypertension Then I think you can go ahead and consider the question of what degree of blood pressure you are going to pay attention to What you want to do is to see to it that these people never develop any changes in one of those three areas

DR CORCORAN Then you are really saying that you should treat the patient before he develops changes in these tests and in the areas that you are evaluating In that case the tests aren t really important as to whether treatment is indicated but rather these tests serve as an indication as to the urgency of blood pressure control and how quickly such control should be effected In other words you will then treat two groups of patients those with already established vascular degeneration and those who are being treated prophylactically against the development of such changes

DR SMITHWICK You ve got to use these tests to prove that they haven t got any changes if you re going to put them into this category for prophylactic treatment

DR MOYER The problem as I see it is how early we start therapy that is prophylactic therapy against these vascular changes If we have a patient who is on placebo therapy being followed carefully who has a persistent blood pressure above 155/95 without evidence of vascular degenerative changes would this case come under the classification of hypertensive disease?

DR DONALDSON Isn t there some adjustment for age? Does anybody want to express an opinion on that as to diastolic pressure?

DR FREIS I think any patient under the age of 35 who has a diastolic pressure of 90 or above on repeated taking certainly ought to be very carefully investigated for renal disease and then treated

DR CORCORAN Your cut off for age would be different in the two sexes too wouldn t it? It would be different for males and females

DR FREIS I think the cut-off for age in the male would be closer to 45 the cut off for age in the female 35 Then I would treat patients with a diastolic pressure of 90 millimeters or above when the age is below 35 in the female and 45 in the male I think that above this age I would not treat until the blood pressure was above 100 millimeters of mercury Patients with pressures above 100 millimeters of mercury are probably deserving of therapy up to 65 or 70 years of age

DR. HOLLANDER If we accept the thesis that as the blood pressure increases with age there is an increased morbidity and mortality rate associated with

the increase in blood pressure then I think the conclusion to be drawn is that we should treat everyone who has an elevated blood pressure in the hope of preventing these complications I dont know whether the panel agrees or not

DR CORCORAN The mild hypertensives in the Framingham survey show a two or threefold increase in mortality and morbidity due to coronary artery disease and most of these patients had normal electrocardiograms when they were initially seen three or four years before

DR MOSER In our definitions of which patients we would recommend for therapy we should introduce another factor and that is the racial difference In the colored population certainly hypertension is a more serious disease If the diastolic is over 90 millimeters of mercury we should certainly be serious about drug therapy in this group of people This includes both males and females

DR MOYER Now may I draw a conclusion? Most of the discussion has centered around specific antihypertensive therapy in the group of patients with diastolic pressures irrespective of age between 90 and 100 millimeters of mercury We conclude that a patient who has been followed on placebo therapy for three to four weeks and who has been checked repeatedly with or without home blood pressures (Dr Freis would prefer home blood pressure as well as some other members of the panel) and who has a diastolic pressure on numerous occasions above 100 millimeters of mercury is deserving of therapy There seems to be no question that this is classified as hypertensive disease deserving treatment Is everyone in agreement?

DR SMITHWICK Hypertension not necessarily hypertensive vascular disease

DR MOYER Hypertension—agreed

DR SCHROEDER When you say therapy you mean that in the broadest possible sense of the word

DR MOYER Yes Im calling this a syndrome now so that we can move on into the more specific therapeutic aspects

DR GROLLMAN May I add to that, Dr Moyer? It seems to me that there is one point that we are not considering and that is what you might define as the art of medicine namely that in a given patient you add a certain decision which comes from your own evaluation I think that there are patients some of my colleagues for example who come into the office with a history suggestive of coronary disease in the family and have hypertension I might treat them with a diastolic pressure of 90 millimeters of mercury On the other hand a patient seen in the clinic a laborer or a woman who is obviously volatile in her reactions I might pass over at 110 millimeters of mercury I think regardless of what we decide that we make certain decisions subject to our own evaluation

DR MOYER Perhaps we should list some manifestations which would

make us be more likely to treat even a milder case Dr Grollman has listed family history of hypertensive disease and Dr Freis has said that when the patient is a female below the age of 35 or a male below the age of 45 he might treat such a patient even if the diastolic pressure is less than 100 millimeters but more than 90 millimeters of mercury Are there any other manifestations that would make us treat patients with the mildest type of disease?

DR SMITHWICK So far as family history goes I think it s been shown that it s important to study both sides of the family that there is a much higher incidence of this difficulty in offspring of parents who come from families where both parents have it than if one has it and not the other And the lowest incidence is always where there is no history on either side of the family I think that has been pretty well established

DR FREIS I just want to express a dissenting opinion I think that there are millions of patients in this country probably who would fulfill your criteria for treatment that I wouldn t treat These are the ones who respond very well to Rauwolfia because you re treating their office blood pressures In other words you re basing your indication for therapy on office blood pressures of 100 millimeters of mercury or more on three visits I don t think you ever get an accurate blood pressure in the office

DR HOLLANDER Dr Freis what makes you feel that the blood pressure taken at home reflects the actual blood pressure of the individual and that the blood pressure under stress perhaps is not more important than the blood pressure that he has in the home? Why don t you use the Sodium Amytal test to determine his actual blood pressure or perhaps anesthesize the patient? Or better yet why don t you take the blood pressure while the patient is asleep and use that?

DR FREIS I think maybe you ought to average them all if you could That would be a good idea because it is the average pressure that counts But it is a strange thing that the blood pressures that have been taken on people at work and on people who have gotten upset at work and are angry at work don t show much of a rise It is only when they are fearful apprehensive when there is a threat to their existence in some way implied or otherwise that the blood pressure goes up The word stress" does not cover the type of emotion that raises blood pressure

DR HOLLANDER I don t believe that

DR MOSER I think that Dr Hollander has a very good point here We know what the average or normal blood pressure is on the basis of many of the readings that all of us take every day and that have been compiled through the years For some reason the people who have high blood pressures in our office or at the Pentagon or in a hospital are a little bit different And I m not certain that we should throw out the office blood pressures taken by physicians in evaluating a patient I think that the elevated blood pressure in the office is a very important thing whether it is stress *per se* or whether it is the cold pressor response or whether it is just a reaction to the sphygmomanometer I think that an increase in arterial pressure is im

TREATMENT OF MILD AND MODERATELY SEVERE HYPERTENSION

DR MOYER Dr Freis if you will outline your classification of mild and moderately severe hypertension we can use this as a basis for our discussion of specific therapy

DR FREIS For severe disease the basal diastolic pressure would be 120 mm of mercury or more I am referring to pressures taken in the home or in the hospital The optic fundi are grades II III or IV The heart should show evidence of hypertrophy not necessarily electrocardiographic evidence but there should be evidence of hypertrophy and dilatation There should be some degree of albuminuria as evidence of renal derangement PSP excretion should be affected—that is below 25 per cent in 15 minutes or below 45 or 40 per cent in three hours

DR MOYER Dr Smithwick disagrees

DR SMITHWICK I would say below 50 per cent in two hours I think 40 per cent is pretty bad Of course 25 per cent in 15 minutes is a more valuable estimate

DR MOYER The group of patients with less severe disease are the mild to moderately severe according to your classification?

TABLE 1 OUTLINE OF TREATMENT FOR ESSENTIAL HYPERTENSION
By EDWARD FREIS M D

I *Cases Generally Excluded from Antihypertensive Treatment*
- A BUN above 70 mg per cent in the absence of congestive heart failure
- B Patients over age 70 years unless diastolic pressure is quite high
- C Home or hospitalized blood pressures normal (diastolic below 90 mm Hg) with no signs of organic damage

II *Treatment of Mild and Moderate Hypertension*
- A Chlorothiazide 500 mg twice daily as initial therapy
- B 1 If blood pressure not controlled after one week of chlorothiazide add reserpine 0 25 mg or alseroxylon (Rauwiloid) 2 mg twice daily for one week then once daily
  - 2 Next week add hydralazine (Apresoline) 25 mg three times daily by the oral route in sequential fashion i e 25 mg once daily for first 2 days 25 mg twice daily for next two days and then 3 times per day
  - 3 If necessary raise hydralazine dosage to 50 mg given 3 times daily Do not exceed 150 mg per day for long term therapy or 300 mg for short term therapy of less than 2 months duration
- C If blood pressure is not controlled continue therapy with home blood pressure checks twice daily for 2 weeks unless this has already been done
- D If home or office blood pressures are well controlled withdraw Rauwolfia after one month Restore drug only if blood pressure rises again
- E If blood pressure is not controlled with combination of hydralazine chlorothiazide and Rauwolfia discontinue hydralazine but continue chlorothiazide and Rauwolfia and
  - 1 Add ganglion blocking drug as follows
    Pentolinium tartrate (Ansolysen) 20 mg after breakfast at 2 P M and at bedtime or chlorisondamine (Ecolid) 10 to 20 mg or mecamylamine (Inversine) 1 25 mg as above
  - 2 Using home pressures as a guide raise dosage by following increments 20 mg of pentolinium or 10 mg of chlorisondamine or 1 25 of mecamylamine every 2 to 3 days until blood pressure falls

make us be more likely to treat even a milder case Dr Grollman has listed family history of hypertensive disease and Dr Freis has said that when the patient is a female below the age of 35 or a male below the age of 45 he might treat such a patient even if the diastolic pressure is less than 100 millimeters but more than 90 millimeters of mercury Are there any other manifestations that would make us treat patients with the mildest type of disease?

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portant as long as we are not using ganglion blockers in these people That would influence our treatment a great deal I m not certain that these office blood pressures taken under stress aren t the ones that we should be treating and should be the pressures we are aiming to lower

Dr Ford I agree with you

Dr Corcoran I would just like to add one note When we tried to associate blood pressure levels with the severity of the other evidences of hypertensive vascular disease the correlation with the office pressure was remarkably poor as compared with the home pressures or with hospital pressures taken by nurses

Dr Meilman Any of you who work on obstetrical services have been aware I am sure of the marked difference of blood pressure when the obstetrician takes it and when the nurse takes it I ve heard many obstetricians say that nurses can t take blood pressures

The people who have the high blood pressures in your office are the ones who outlive the doctor because they have been intermittently normotensive all their lives In other words they have done for themselves what we try to do with our drugs Now if you are going to pay attention to the office blood pressure in these people you might just as well pay attention to the peak blood pressure on ganglionic blockade drugs instead of a low blood pressure We know that if you can lower the pressure intermittently that does the job and if these people do it alone and many of them do they treat themselves

Dr Smithwick I would like to agree with that statement People who have intermittent reduction of pressure to normal levels a large part of the time have a good deal of protection against the disease I think the two best ways to decide about the severity of hypertension are home blood pressure levels and pressures at bed rest in a hospital taken by a technician And you don t have to leave the patient in bed for months either Twenty four to 48 hours is plenty of time for this evaluation If in addition to the blood pressure returning to normal under these circumstances there is nothing wrong with his eyes heart or kidneys then I think you re safe in saying that this patient has not as yet reached the stage of persistent hypertension If he has reached the stage of persistent hypertension then he ll surely get into trouble

Dr. Corcoran After the third day in the hospital patients generally stabilize at some reasonable level comparable to home pressures

Dr Smithwick You don t have to make it a long session

Dr Finnerty From the practical standpoint I would say that the home blood pressures will give you a good index of the severity of the vascular disease Let us go back one step further for the doctor who is out in practice and for the "millions of people" who would fulfill these criteria When does the doctor give the patient a blood pressure cuff? What do we tell the doctor? What is his guide? Which patient does he give the blood pressure cuff to?

Dr Moyer Who are the strong advocates here of blood pressure cuffs? I suppose Dr Freis will have to answer that one He probably gives them to all of his patients

Actually in the practice that Dr Ford and I had prior to my coming to Philadelphia I suspect that about one fourth to one half of the patients were given sphygmomanometers and this was primarily for investigational purposes in our research projects on antihypertensive drugs I think that this aspect may have been underestimated here Are the home blood pressures advocated for investigational purposes or because they are necessary for adequate treatment of the patient? There is also a very definite group of patients who just don t do well with the sphygmomanometer If taking pills is bad or a nuisance for some patients taking the blood pressure several times each day is worse

Dr Freis I would think that there aren t many of them the number is very small in our experience It s surprising how many of these patients are not bothered by sphygmomanometers As a matter of fact they lose their *apprehension about taking blood pressure*

When I examine a middle aged female patient and fundi are normal and there is no albumin in the urine then I say Well I don t think you really have a high level of blood pressure all the time and we will teach your husband how to take your blood pressure at home and lend you a cuff for two weeks This usually solves a very difficult treatment problem Now in a young person in his thirties or younger this may not be necessary One can pretty well assume that this person either has hypertension or is going to get it It is the middle aged group with which you have the difficulty

Dr Moyer I think this matter of home blood pressure is on dead center I will conclude by polling the panel Will each man raise his hand to the following question if it applies to him How many of you use home blood pressures in 80 per cent or more of your patients with suspected hypertension *that is you give the patient or his family a sphygmomanometer?*

Only two of the 16 panelists use home blood pressures in 80 per cent or more of their patients with hypertension This is surprising I thought the discussion indicated that many of you used home blood pressures in all but the occasional patient

Now how many give a sphygmomanometer to more than 50 per cent of *your patients?*

Three panelists

How many use it in more than 25 per cent and less than 50 per cent?

There are three

How many use it only very occasionally that is for an occasional problem?

Two panelists

How many don t use it at all?

Six panelists don t use home blood pressure recordings at all Now you can get a general idea of what goes on among the therapists Dr Freis and Dr Perry use home blood pressures for a rather comprehensive evaluation of the diastolic pressure The other panelists are not quite as enthusiastic

TREATMENT OF MILD AND MODERATELY SEVERE HYPERTENSION

DR MOYER Dr Freis if you will outline your classification of mild and moderately severe hypertension we can use this as a basis for our discussion of specific therapy

DR FREIS For severe disease the basal diastolic pressure would be 120 mm of mercury or more I am referring to pressures taken in the home or in the hospital The optic fundi are grades II III or IV The heart should show evidence of hypertrophy not necessarily electrocardiographic evidence but there should be evidence of hypertrophy and dilatation There should be some degree of albuminuria as evidence of renal derangement PSP excretion should be affected—that is below 25 per cent in 15 minutes or below 45 or 40 per cent in three hours

DR MOYER Dr Smithwick disagrees

DR SMITHWICK I would say below 50 per cent in two hours I think 40 per cent is pretty bad Of course 25 per cent in 15 minutes is a more valuable estimate

DR MOYER The group of patients with less severe disease are the mild to moderately severe according to your classification?

TABLE I OUTLINE OF TREATMENT FOR ESSENTIAL HYPERTENSION
By EDWARD FREIS M D

I *Cases Generally Excluded from Antihypertensive Treatment*
- A BUN above 70 mg per cent in the absence of congestive heart failure
- B Patients over age 70 years unless diastolic pressure is quite high
- C Home or hospitalized blood pressures normal (diastolic below 90 mm Hg) with no signs of organic damage

II *Treatment of Mild and Moderate Hypertension*
- A Chlorothiazide 500 mg twice daily as initial therapy
- B 1 If blood pressure not controlled after one week of chlorothiazide add reserpine 0 25 mg or alseroxylon (Rauwiloid) 2 mg twice daily for one week then once daily
  - 2 Next week add hydralazine (Apresoline) 25 mg three times daily by the oral route in sequential fashion i e 25 mg once daily for first 2 days 25 mg twice daily for next two days and then 3 times per day
  - 3 If necessary raise hydralazine dosage to 50 mg given 3 times daily Do not exceed 150 mg per day for long term therapy or 300 mg for short term therapy of less than 2 months duration
- C If blood pressure is not controlled continue therapy with home blood pressure checks twice daily for 2 weeks unless this has already been done
- D If home or office blood pressures are well controlled withdraw Rauwolfia after one month Restore drug only if blood pressure rises again
- E If blood pressure is not controlled with combination of hydralazine chlorothiazide and Rauwolfia discontinue hydralazine but continue chlorothiazide and Rauwolfia and
  - 1 Add ganglion blocking drug as follows Pentolinium tartrate (Ansolysen) 20 mg after breakfast at 2 P M and at bedtime or chlorisondamine (Ecolid) 10 to 20 mg or mecamylamine (Inversine) 1.25 mg as above
  - 2 Using home pressures as a guide raise dosage by following increments 20 mg of pentolinium or 10 mg of chlorisondamine or 1 25 of mecamylamine every 2 to 3 days until blood pressure falls

3 Treat side effects as they arise as follows
a Constipation Cascara sagrada and/or milk of magnesia at bedtime Neostigmine (Prostigmin) orally in dose of 15 to 30 mg on arising if laxatives are ineffective
b Sunglasses and inexpensive dime store reading glasses for disturbed visual accommodation
c For dry mouth try pilocarpine nitrate orally in a 5 mg dose hour before meals
d If unsuccessful reduce dosage of ganglion blocking agent a little If this is ineffective switch to another blocking drug

4 After 3 months of adequate blood pressure control (average reduction of 20 per cent or more of mean pretreatment blood pressure) try withdrawing Rauwolfia After 6 months try withdrawing blocking agent

Note In all chlorothiazide treated patients serum potassium levels should be checked one and 3 months after starting the drug and then every 6 months thereafter If potassium level falls below 3 5 mEq /L add 75 mEq of supplementary potassium daily Digitalis toxicity is frequent unless potassium supplements are given

III *Treatment of Severe Hypertension*

A Hospitalize patient and record blood pressure 4 times daily

B 1 If diastolic is above 140 mm Hg give 2 to 4 mg of reserpine intravenously every 4 to 12 hours depending on need If BUN is below 70 mg per cent but above normal add chlorothiazide 500 mg twice daily and hydralazine 25 mg three times daily elevating dosage to 50 mg after 48 hours If diastolic blood pressure falls to 120 mm Hg or less follow BUN and lighten treatment if latter is rising If BUN stabilizes below 70 mg per cent add ganglion blocker raising dosage daily and recording blood pressure in supine dangling and standing positions Repeat the BUN every 48 hours Aim for gradual reduction of blood pressure When reduction in blood pressure is achieved substitute oral for parenteral reserpine and in lower dosages (0 25 mg once or twice daily) for maintenance

2 If BUN is in normal range begin chlorothiazide hydralazine and blocking drug simultaneously but proceed cautiously with frequent checks of BUN after diastolic falls to 120 mm Hg or less

3 If control diastolic pressure is below 140 mm Hg but more than 120 mm Hg begin with oral rather than parenteral reserpine but otherwise proceed as outlined above

IV In the unresponsive unreliable or uncooperative patient below age 45 with basal diastolic pressure above 110 mm Hg and adequate renal function (no azotemia and PSP above 15 per cent in 15 minutes or 35 per cent in 2 hours) refer for surgical sympathectomy and if necessary follow up treatment with chlorothiazide

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DR FREIS Yes They have some but not all of the above criteria

DR MOYER Will you outline your treatment program for mild and moderately severe disease?

DR FREIS I begin therapy in mild and moderately severe hypertension with chlorothiazide (Table 1) and if I do not get a reduction of blood pressure within a week I add Rauwolfia using either reserpine 0 25 mg twice daily or alseroxylon (Rauwiloid) 2 mg twice daily for one week This is largely premedication for getting them started on hydralazine (Apresoline) Then I begin hydralazine Our usual procedure is to begin the dosage of hydralazine in sequential fashion in order to avoid the acute side effects that is begin with 10 to 25 mg once daily for two days then twice daily for two more days and then three times daily

DR. MOYER To what level should the blood pressure be reduced?

DR FREIS In the mild and moderate cases I wish to lower the home blood pressures to normal

DR MOYER Normal is a diastolic below 100 mm Hg?

DR FREIS The average diastolic pressure should be reduced below 90 mm Hg in the upright position If the response is not adequate after taking 25 mg of hydralazine three times a day for two weeks then increase the dose to 50 mg The patient is then getting a total of 150 mg per day If the blood pressure is still not controlled then I will usually go ahead and add one of the ganglionic blocking agents and titrate the patient in the manner that is shown in Table 1 When this is done and the response to hydralazine is not striking I discontinue the hydralazine

DR MOYER May I ask you why you do not advocate a dose of hydralazine in excess of 150 mg per day?

DR FREIS Well I've been using hydralazine since it came out in 1951 and I have not seen the disseminated lupus type of reaction For the reason that it might appear with higher dosages only I think it is safer to use a gan glionic blocking agent than to push hydralazine to the point at which you may get this hydralazine syndrome It is a matter of safety In addition I have a distinct impression that doubling the dose from 150 to 300 mg per day does not increase the antihypertensive effect in the vast majority of patients Perhaps if you went still higher you might but I think to go still higher is quite dangerous

DR MOYER I think this latter point is important However I vaguely re member that Dr Corcoran at one time said that "hydrazaline disease" or the lupus syndrome does not occur if the dose is not in excess of 400 mg per day

DR CORCORAN We have not seen it in people who have been kept on 600 mg for a month The dose in these patients was then reduced stepwise from 500 to 400 and then to 300 mg per day I think there is an increased effect Dr Freis as you go from 300 to 600 mg per day I doubt that there is much increase going from 150 to 300 mg per day If a blood pressure effect can be obtained much smaller doses can maintain the effect as time goes on We do not keep people on 600 mg daily for months on end We keep them on 600 mg daily for no more than six weeks and we have not seen the disease under this circumstance

DR MOYER May we ask Dr Freis if he would object to stepping up the dose say to 300 or 400 mg a day to break the blood pressure and after these doses have brought the pressure down then to back titrate after two or three weeks or a month to the smaller 150 mg dose?

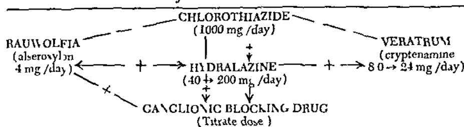
DR FREIS No That would seem a very reasonable thing to do I would have no objection to that at all

DR MOYER I think Dr Gifford has slightly different ideas about this Would you object to this general approach to treating a patient?

DR GIFFORD In general I think Dr Freis and I agree We both start off with chlorothiazide (Table 2) I have not found it necessary to prepare the

TABLE 2 PLAN OF TREATMENT OF THE AMBULATORY PATIENT WITH HYPERTENSION

By RAY GIFFORD M D



patient with a Rauwolfia preparation in anticipation of giving hydralazine Our side reactions to hydralazine have not been serious when the patient has been taking chlorothiazide for a week or two Ordinarily if the combination of hydralazine and chlorothiazide is not sufficient to reduce the blood pressure to levels that I consider desirable I progress right to a ganglion blocking agent rather than try to add Rauwolfia or Veratrum to the therapeutic program There are exceptions to this My colleagues use more Rauwolfia than I do I increase the dose of hydralazine up to 75 mg four times a day or to a total of 300 mg per 24 hours I recognize that we are running some risk of the hydralazine mesenchymal reaction We have seen it in one patient who was taking a dose of 200 mg a day but by and large it was those patients who were taking more than 400 mg a day who developed this syndrome Personally I think I would rather have hydralazine disease than a reserpine depression You can get over hydralazine disease but sometimes it takes a long time to get over reserpine depression

When hydralazine is not effective I discontinue it and start the patient on a ganglionic blocking agent, while continuing the chlorothiazide The dose of the blocker is titrated as indicated by Dr Freis

Patients with severe hypertension are started out on a combination of chlorothiazide and a ganglionic blocking agent immediately without the intermediate step of hydralazine

DR MOYER One of the problems in patients that I have given hydralazine to has been palpitations and tachycardia This reaction is even more annoying to the patient than the headache One of the best ways that we have found of getting around it has been premedication with Rauwolfia as Dr Freis has pointed out As a matter of fact it reduced the incidence to 10 per cent as compared to 40 or 50 per cent when we gave hydralazine alone in one of our studies Does chlorothiazide significantly alter this reaction? I would raise that question for discussion between you two because this is one thing that makes a patient stop taking the drug without hesitation When his heart starts pounding and he gets short of breath and develops tachycardia he is unhappy

DR. GIFFORD I agree entirely Until we began to use chlorothiazide routinely in starting patients off on treatment we did prepare patients with one

of the Rauwolfia preparations just for that reason that is to reduce the incidence of tachycardia and palpitation when hydralazine was started However in the last six months we have omitted that and simply prepare the patients with chlorothiazide I don t believe that we have any more trouble with hydralazine than we did when we were preparing them with Rauwolfia

DR FORD We prepare our patients with both chlorothiazide and Rauwolfia before starting hydralazine (Table 3) Our results with hydralazine have not been encouraging even when given in combination with chlorothiazide and Rauwolfia The combination of chlorothiazide and Rauwolfia given in combination with mecamylamine is much more effective at least in the patients with more severe disease that we treat

TABLE 3 OUTLINE OF DRUG THERAPY OF THE AMBULATORY PATIENT WITH HYPERTENSION

By RALPH V FORD M D

DEGREE OF HYPERTENSION	FIRST DRUG TO BE GIVEN	IF NOT EFFECTIVE IN REDUCING MBP MORE THAN 20 MM MERCURY ADD FOLLOWING
Mild labile	Chlorothiazide*	Rauwolfia
Mild stable	Chlorothiazide + Rauwolfia†	Hydralazine‡
Moderate	Chlorothiazide + Rauwolfia	Hydralazine and/or ganglionic blocker§
Severe	Chlorothiazide + Rauwolfia	Ganglionic blocker§

Dose is 500 mg twice a day

† Alseroxylon dose is 2 mg four times a day for one week then reduce to twice a day

‡ Start with 25 mg four times a day and increase at weekly intervals

§ Start with 1 25 mg of mecamylamine or 20 mg of pentolinium with each meal and increase the dose progressively until the desired reduction in blood pressure has been obtained

DR CORCORAN While we are on the topic of hydralazine tachycardia we have not been satisfied that either Rauwolfia or chlorothiazide obviated the tachycardia when we used doses of hydralazine up to 600 mg per day Dr Wilkins has had a good deal of experience with protoveratrine as an agent for controlling hydralazine tachycardia and thinks that it is pretty effective Has anyone else had experience with the use of Veratrum drugs as an antidote for the tachycardia of hydralazine?

DR MOYER I tried it at one time but not in combination with chlorothiazide It was not very effective under those circumstances

DR CORCORAN A few patients that I observed taking this combination were not doing too well

DR HOLLANDER In our clinic (in preparation for the use of hydralazine) we like to prime the patient with both Rauwolfia and Veratrum to protect him against the fast pulse that hydralazine produces I think a word of caution is in order at this time about the use of hydralazine in the older age group One must be cautious because these people may have unsuspected coronary artery disease We as well as other investigators including Dr Moyer have shown that hydralazine (Apresoline) is a potent angina

producing compound. We compared the ability of hydralazine to produce angina with the standard exercise test and found that hydralazine is a more sensitive test for coronary insufficiency; therefore one should be cautious in the older age group and not use hydralazine indiscriminately.

DR. CORCORAN: We had two sudden deaths in our early experience with hydralazine which rather convinced us that it is not only a sensitive test but maybe it is a little too sensitive at times in these old people.

DR. FREIS: What dosage was that, Dr. Corcoran?

DR. CORCORAN: That was when we were using 800 to 1200 mg.

DR. HOLLANDER: We had a few myocardial infarctions, Dr. Freis, but we have not had any deaths from the use of hydralazine.

TABLE 4. OUTLINE OF DRUG TREATMENT OF ARTERIAL HYPERTENSION
By WILLIAM HOLLANDER, M.D.

		DRUGS TO BE GIVEN IN SEQUENTIAL FASHION
I. Arterial hypertension without advanced vascular complications	1	Rauwolfia
Diastolic blood pressure usually below 125 mm Hg	2	Veratrum
Fundi less than grade III retinopathy	3	Hydralazine
	4	Chlorothiazide
	5	Ganglionic blockers
II. Arterial hypertension with advanced vascular complications		
Diastolic blood pressure frequently above 120 mm Hg		
Fundi grade II to IV retinopathy		
(1) Severe or malignant hypertension	1	Rauwolfia
	2	Veratrum
	3	Hydralazine
	4	Chlorothiazide
	5	"Ganglionic blockers
(2) Cerebral vascular disease	1	Rauwolfia
	2	Veratrum
	3	Hydralazine
	4	Chlorothiazide
(3) Coronary artery disease	1	Rauwolfia
	2	Veratrum
	3	Chlorothiazide
	4	Iproniazid
(4) Chronic congestive heart failure	1	Digitalis
	2	Chlorothiazide with or without mercurials
	3	Rauwolfia
	4	Hydralazine
	5	"Ganglionic blockers"
(5) Paroxysmal nocturnal dyspnea	1	Chlorothiazide
	2	Mercurials
(6) Renal insufficiency	1	Rauwolfia
	2	Veratrum
	3	Hydralazine
	4	Chlorothiazide

For details of drug administration see pages 399-408, 570, 580.

DR MOYER Just to re emphasize the point that Dr Freis has raised relative to Rauwolfia most of the depressive reactions have come after the patients have been on Rauwolfia for a prolonged period of time The pharmacology of hydralazine is such that the tachycardia the increase in renal blood flow and the increase in cardiac output are temporary phenomena Usually this effect is lost within two to three weeks after initiating a set dose of the drug so that if you could premedicate a patient with Rauwolfia you would fairly well circumvent this problem in a fair percentage of patients

DR HOLLANDER I think we should probably include Veratrum especially if the pulse rate is fast and hasn t been slowed down with Rauwolfia and we are considering the use of hydralazine Then I would think that Veratrum should be the next step (Table 4)

DR CORCORAN Do you continue the reserpine when you are using Veratrum?

DR HOLLANDER We institute Rauwolfia and if the pulse rate is still fast then it would seem rational to institute Veratrum (Table 4) to slow the pulse rate in preparation for the use of hydralazine

DR MOYER In other words we can say that we would start a patient on therapy with chlorothiazide and Rauwolfia and then after a week or two of Rauwolfia therapy we would add hydralazine If a tachycardia developed as an untoward effect from the hydralazine then Dr Hollander would try Veratrum to block off primarily the tachycardia associated with hydralazine I m certain that nobody here would object to that

DR CORCORAN The Rauwolfia would be continued throughout am I right?

DR MOYER Yes

DR FINNERTY I would like to take issue concerning the large group of patients with anxiety I don t see what chlorothiazide as the initial therapy is going to do for this It seems that the panel is not composed of Rauwolfia users I ll make a plea for Sodium Amytal three times a day as a start to therapy What does the panel think about this? If these patients basic disease is anxiety then I think that the basic treatment should be toward relief of anxiety and Rauwolfia or a sedative should be the basic medication

DR HOLLANDER I myself start treatment with Rauwolfia (Table 4) and I would use chlorothiazide after that for the reason that Dr Finnerty has stated

DR MOYER Can we say then that there are a certain number of patients who have rather marked anxiety manifestations (whether this be hostility or fear as Dr Freis has indicated) and who are hyper reactive to certain situations? These patients need drugs which are not specifically antihypertensive such as Sodium Amytal or perhaps Rauwolfia When the blood pressure does not respond adequately then they should be placed on the standard program as outlined above Is there objection to this approach? Dr Freis?

DR. FREIS It's rather interesting that people who don't use home blood pressure recordings very much talk about the use of Rauwolfia and Sodium Amytal first I defined these patients as those whose home blood pressures are elevated and in those individuals I don't find that sedative and tranquilizing drugs are very valuable I think these drugs are very valuable in the patient who has normal pressures at home but who has elevation of pressure in the doctor's office

DR. MOYER Actually Dr Finnerty is treating a specific problem that is not necessarily related to the blood pressure He is adding an adjunctive type of therapy for treating this patient's anxiety symptoms and the blood pressure just happens to be an added phenomenon

DR FINNERTY That is correct

DR MOYER Dr Smithwick raises the question as to the dose of chlorothiazide He thinks that the dose of 500 mg given twice a day may be large Is that the usual dose of this diuretic that the panel members employ?

DR CORCORAN 250 mg three times a day is more common in our clinic given for five days a week

DR DONALDSON Is there any reason to use it three times a day rather than at twelve hour intervals? If you follow the pharmacology of the drug from the standpoint of sodium excretion and diuresis the twelve hour interval seems to be about the most logical Is that true or not true Dr Moyer?

DR MOYER I think that is true There is one thing that bothers me about Dr Corcoran's suggestion and that is his treatment for five days only out of each week especially when giving chlorothiazide in combination with potent agents such as the blocking agents The blood pressure effect will occasionally be lost over that two or three day interval

DR CORCORAN This is not a solid or firm recommendation It is a regimen which we were trying out at the time There are very few patients on persistent daily chlorothiazide

DR MEILMAN One of the difficulties of giving chlorothiazide twice a day is that the second dose is often given late in the evening and these patients will suddenly develop nocturia when they have never had it before You can get the same effect I think if you give 0 5 gm twice daily but earlier in the day

DR MOYER If you are giving chlorothiazide continuously they have to get water in order to diurese So why not just restrict water intake in the evening? You are probably talking about cardiacs really and not hypertensives Is that right?

DR. MEILMAN I think that I have seen patients who were hypertensives who complained that they had to get up at night They were all in the age group where other factors may be involved such as prostatic hypertrophy A lot of patients can get along with just one daily dose in the morning and maintain the good effect

DR MOYER Dr Freis did you have something you wanted to say?

DR FREIS In our studies when we withdrew chlorothiazide and the patients were allowed to eat salt they would very rapidly gain weight and their elevated blood pressure would return Certainly within 48 hours this would happen and often within 24 hours It has always been my impression that you had to keep the dosage up every day If you did not do this it was a rather dangerous proposition I must admit that in regard to potassium it would be safer if you could follow an intermittent dosage program because you would get potassium repletion during the period of vacation from the drug But the effect on the blood pressure is not very good and I think it is a little hazardous to do this especially in a severe hypertensive

DR CORCORAN Well then don t we have to ask ourselves before we start out with this initial chlorothiazide what diet these patients are going to be on? Are you going to restrict salt or not? We do

DR FREIS If you are going to have them on a really strict low salt diet you are doing away with one of the great advantages of chlorothiazide Certainly the more you restrict the salt intake the more feasible an intermittent dosage schedule of chlorothiazide would be You can trust the patient with pills but I don t trust him in regard to salt intake

DR HOLLANDER Dr Freis I can t completely agree with you about how quickly the blood pressure returns to pretreatment levels following the withdrawal of chlorothiazide especially when it is being given in combination with the milder antihypertensive drugs that is Rauwolfia and hydralazine It has been our experience that when you withdraw chlorothiazide from a combination of Rauwolfia and hydralazine the blood pressure does not come back to pretreatment levels in two days It might take anywhere from one to four weeks before the blood pressure returns to control values Now it might very well be that with ganglionic blocking agents when you withdraw chlorothiazide the blood pressure abruptly returns It may overshoot the control value I would also agree that when using ganglionic blocking agents if you withdraw the chlorothiazide you might get into serious difficulty

DR MOYER You would agree Dr Freis that this breakthrough is probably based on the severity of the hypertension and that if you are treating the milder group who are only receiving chlorothiazide plus Rauwolfia the possibility of breakthrough would be much lower whereas if you had a more severe hypertensive who is receiving more potent therapy they are liable to escape rather rapidly when chlorothiazide is discontinued?

DR FREIS Yes you could try an interrupted schedule but I would think it would be very important to check the blood pressure when you do so If we are trying to moderate the hypertension we should be very careful not to let the blood pressure escape one day in the week It should be kept down all the time

DR MOSER I would just like to reiterate what Dr Freis has said We tried this weekend routine five days on chlorothiazide and two days off in a group of patients who had been maintained on ganglion blockers and found that

escape was very rapid—sometimes within 16 to 24 hours But when they took their chlorothiazide again on Monday morning blood pressure controls re established very quickly There is no question that when patients are on ganglion blockers they should be maintained on chlorothiazide continu ously With regard to the salt intake there is evidence that on an average American diet of 8 to 10 gm of salt a day chlorothiazide is effective There is much debate as to whether or not patients taking in more salt than that that is 15 gm or so may not break through the chlorothiazide effect At present it is something that is unsettled but on the average American diet it appears that they do not have to restrict salt very much

Dr Moyer I think this is a point to poll the panel How many keep their patients who are not in heart failure on diets below 2 to 3 gms of salt when giving chlorothiazide? Apparently none of the panelists use strict low salt diets of this degree

How many keep their patients on a diet at all relative to salt intake?

Dr Moser I just tell them not to add salt to their food

Dr Moyer Is that the general concensus? How many keep their patients on a salt intake of 3 to 6 gm? Actually a diet containing this much salt is merely a diet taking away the bacon the salt shaker salty food and a few other salty things and this is about all there is to it Apparently most of the panelists follow this technique

Dr Freis do you want to indicate exactly what your restrictions are?

Dr. Freis I just tell the patient to avoid salted foods

Dr Hollander Why?

Dr Freis Why not? I think you showed in your first paper Dr Hollander that if you put a patient on a low sodium diet the effect of the chlorothiazide is enhanced Don t you believe that any more?

Dr Hollander Certainly I do But this is not comparable to what we are talking about In the original description of the effects of sodium intake this is what we found that patients who were on a regular salt diet who were resistant to chlorothiazide responded when the sodium intake was restricted However on a regular salt diet if you get a response you usually don t get any greater response when you reduce the sodium intake to a level that you are now talking about that is 3 to 4 gm So it would seem to me that actu ally there is no rationale for moderately restricting the sodium intake We are under the impression that if you restrict the intake of sodium this pre disposes to more disturbances in the blood chemistries while taking chloro-thiazide

Dr Moyer Can we conclude that the salt intake should be less than 6 or 8 gm per day? Obviously there are some patients who really take a lot of salted foods and I believe it has been shown that if you take in amounts of 14 to 15 gm you do break through the antihypertensive effect of the drugs as Dr Moser indicated Therefore it seems that we should perhaps at least keep the dose of salt per day restricted below this level Is that a fair con clusion?

DR FREIS I agree and I also am in agreement with Dr Hollander that is not to reduce the salt intake to the point where you make the patient s life uncomfortable I think that is the important point

DR HOLLANDER That is why we are so enthusiastic about chlorothiazide because the patient does not have to suffer too much

DR MOYER How many panelists use a dose of chlorothiazide of 500 mg twice a day? All but three

DR CORCORAN We use 500 mg twice a day but to people taking ganglion blockers we give 250 mg three times a day

DR. HOLLANDER We use chlorothiazide in much smaller doses than 750 mg a day when combined with other drugs We have patients receiving chlorothiazide in a dosage as small as 125 mg a day or 125 mg twice a day in a combination with other drugs with very impressive results I think that the objective actually should be to reduce the dosage of chlorothiazide whenever possible because at the lower dose level there is no question that this compound does not produce the disturbance in electrolytes and BUN that it does in higher dose range

DR MOYER You suggest that we could use a dose of 500 mg twice a day as a starting dose to get our various drugs adjusted and then back titrate the dose to the minimum effective dose of the diuretic which maintains the blood pressure?

DR HOLLANDER Agreed

DR MOYER Dr Freis you don t object to that do you? I believe that this approach is a relatively sound pharmacological principle is it not?

DR FREIS Yes

DR. SMITHWICK Could I say a word? This has nothing to do with a discussion of surgery but I would like to say one word of caution If by any chance you are going to treat a patient who has had a splanchnicectomy the chlorothiazide dosage ought to be very much smaller We begin with 62 5 mg and we never start with more than 125 mg We don t increase the dose for a week or two Even on those small dosages we have the feeling that several patients who had been going along pretty well for many years with coronary heart disease and congestive failure died because of chlorothiazide perhaps a result of digitalis intoxication We can t prove that it was due to the drug we strongly suspect that it was

DR. PATON I m just trying to get back to the old pharmacological principle of the therapeutic/toxic ratio that is the ratio when the over all benefits to patients are greater than the loss they suffer I was also hoping that I could get a rough estimate at what level to expect reduction in morbidity and mortality of hypertensives and to compare this with the cost of the medicaments and side reactions so as to decide when treatment for the patients becomes worth while

DR MOYER Allow me to poll the panel? Out of the first 100 patients treated with chlorothiazide by the various members of the panel how many have developed blood dyscrasias purpura serious hypokalemia that has gotten the patient into trouble from digitalis intoxication etc ? Out of 100 patients treated for hypertension how often have these manifestations of toxicity been observed?

DR CORCORAN We have not seen the blood dyscrasias or purpura so far but our group is not very large Dr Gifford had some data on that the other day

DR DONALDSON I have seen none to date

DR MOYER We are talking only of patients with hypertension not cardiac failure and so forth Dr Ford?

DR FORD None

DR MEILMAN We have had three skin rashes and we have had one serious case of hypokalemia with uremia that is four patients out of 200

DR MOSER Four cases of severely low potassium

DR FREIS Wait a minute You said we were not to talk about hypokalemia didn t you?

DR MOYER I said hypokalemia which had caused a serious problem not just a laboratory observation but one which caused digitalis intoxication or other untoward clinical manifestations and occurring in hypertensives

DR FREIS We had a skin rash

DR MOYER How about the rest of you?

DR GIFFORD I have seen one anemia which is well documented as a result of the administration of chlorothiazide and it is interesting that this patient also had previously developed anemia when receiving a sulfonamide preparation for urinary tract infection We have seen one patient with thrombocytopenia without purpura and two patients with purpura without thrombocytopenia The latter two were not hypertensive patients In a group of strictly hypertensive patients out of 150 cases that I reviewed 43 per cent very few of whom were in congestive failure developed a serum potassium level below 3 5 mEq /L sometime during the course of therapy with chlorothiazide Usually it was temporary and tended to return to normal without supplements of potassium even though therapy with chlorothiazide was continued Approximately 12 per cent of these had serum potassium levels at least one time below 3 mEq /L However out of this group only four developed symptoms and what we might interpret as a serious hypokalemia requiring hospitalization and intravenous replacement of potassium on an emergency basis These four were explained as follows One was a patient with severe renal insufficiency and the other three became acutely ill with gastroenteritis in which presumably the loss of potassium was excessive over and above that produced by chlorothiazide A significant observation was

that out of these 150 patients about 23 per cent who started with normal blood ureas developed at some time or other during the course of therapy a blood urea which was distinctly abnormal Here again they tended to return to normal in spite of continuation of therapy with chlorothiazide but a few did not a few had a persistently elevated blood urea so long as chloro thiazide was given and these were patients who started with normal blood urea nitrogens

DR MOYER How often was this an analytical error in the laboratory?

DR GIFFORD I can count on the blood urea concentrations pretty well 40 mg per cent being the upper limit of normal I dont consider the BUN abnormally elevated until it gets above 50 mg per cent I took a similar group of patients treated previously who had normal blood urea nitrogens and who were treated with ganglion blocking agents and out of that group only 4 per cent developed abnormally high blood urea nitrogens during treatment so that I think that rules out laboratory error

DR HOLLANDER I hope we have no laboratory errors in our observations We have recently studied the problem with respect to the effects of chloro thiazide on the blood chemistries We analyzed the serum electrolyte and the BUN in 50 subjects receiving chlorothiazide doing these determinations serially I would just like to review them Serum potassium concentrations in these 50 subjects were appreciably reduced in 40 per cent I mean they had at least a 0 5 mEq /L fall in the serum potassium Twenty five per cent of the group had a marked reduction in the serum potassium to below 3 5 mEq /L In analyzing the data on blood urea nitrogen we found that about 8 per cent of our subjects had a rise in blood urea nitrogen of more than 9 mg per cent The rise in blood urea nitrogen in one individual who had relatively normal function to begin with returned to normal on withdrawing the compound Likewise about 7 to 8 per cent of the group had an apprecia ble reduction in serum sodium that is a drop in serum sodium of more than 9 mEq /L Two subjects had a fall in serum sodium to a level of 125 mEq /L and one to 119 mEq /L Hypochloremic alkalosis occurred in about 8 per cent of the group In trying to determine the factors that predisposed to these changes we came up with the following conditions (1) Restriction of salt intake predisposed to these changes (2) High dosage of the com pound likewise seemed to cause these disturbances in electrolytes (3) Pre existing renal disease was another condition which predisposed to these abnormalities

With regard to other side effects from chlorothiazide I have had five patients who developed skin rashes Most of these rashes have been benign but we think we have seen a case with exfoliative dermatitis from chlorothia zide We have seen purpura in two of our patients but the purpura actually were petechiae and there was no abnormality in the formed elements of the blood Like everyone else we likewise observed digitalis toxicity pre cipitated by low serum potassium One other complication that we have observed is orthostatic hypotension in patients who have a marked dis turbance in serum electrolytes I think this is a sign of some disturbance in the serum electrolytes With the orthostatic hypotension we have observed collapse

DR MOYER We can then conclude that the majority of the investigators here have not seen too many serious side effects In some areas side effects have been fairly frequent and we should be quite cognizant of this problem in treating patients I would gather that in no instance have these side effects been irreversible

DR PERRY Although we haven t seen much trouble people have had some difficulty and I think maybe we ought to look at the other side of the coin Has anyone really ever seen any help from these drugs? I think we have to remember that we are really treating not for the immediate future but for the long range future These are people with mild hypertension whom we are talking about now These people will probably die sometime in the distant future of atherosclerosis rather than hypertension and the best we can say for this therapy is that these drugs will lower blood pressure

DR HOLLANDER That is one of the reasons why we do not advocate chlorothiazide to be used first (Table 4) We do not know what all of these side effects mean We do not know what the changes in blood chemistries mean We agree that they are not clinically detectable but we must consider that chlorothiazide bangs the heck out of the renal tubules and it does it every single day I do not know whether we can conclude that everything will go all right from here on even though clinically these patients seem to be doing all right I think we must be cautious

TREATMENT OF SEVERE HYPERTENSION

DR MOYER I would like to get to another group of patients now the severe group that everybody more or less agrees with Dr Freis should be treated When the diastolic pressure is in excess of 120 mm Hg and particularly if it is fixed when there are changes in the electrocardiogram and changes in the optic fundi and kidneys antihypertensive drugs are indicated Dr Freis how would you approach these patients? We will get into adjunctive therapy with surgery in these patients will we not?

DR FREIS I think these patients deserve hospitalization and when they are hospitalized they should have all the diagnostic tests done to rule out a renal cause of hypertension possibly a remedial type of coarctation a pheochromocytoma and so on Then if no correctable form of hypertension is found and if the diastolic is above 140 mm Hg we would treat them as an acute emergency (Table 1) giving them on admission a dose of 2 to 4 mg of reserpine intramuscularly every four to twelve hours depending on the response of the blood pressure If the blood urea nitrogen is found to be below 70 mg per cent, I add chlorothiazide 500 mg twice daily and hydralazine 25 mg three times daily right away and later increase it to 50 mg

DR MOYER Do I understand that you start all your patients with diastolic pressure above 140 mm Hg on intramuscular reserpine?

DR FREIS Yes that is true If the blood pressure falls to 120 mm Hg or less diastolic we determine the blood urea nitrogen every 48 hours and reduce the dose of hydralazine if the BUN increases If the BUN continues

to rise we reduce the dose of hydralazine so that the blood pressure increases enough to stabilize the BUN If the blood urea nitrogen stabilizes below 70 mg per cent we add a ganglionic blocking agent If the blood pressure has not fallen below 110 mm Hg diastolic the dose is increased daily until the blood pressure in the supine dangling and standing positions is reduced to as low a level as the patient can tolerate The BUN is repeated every few days We aim for a gradual reduction of blood pressure even in the patients with elevated BUN

When the blood pressure is reduced adequately substitute oral reserpine or alseroxylon for parenteral reserpine and in a lower dosage that is 0 25 mg of reserpine once or twice daily or 2 mg alseroxylon twice daily for maintenance so that we gradually get the patient on to a regimen which would be Rauwolfia hydralazine chlorothiazide and a ganglionic blocking agent if necessary (Table 1)

If the BUN is in the normal range all along we would begin again as before with chlorothiazide and hydralazine but we would not wait to give the blocking agent We would begin the blocking agent at the same time we start hydralazine and chlorothiazide proceeding cautiously and following the BUN because some of these patients will show an elevation of BUN as their blood pressure falls even though it was not elevated to begin with Lighten up on treatment and let the blood pressure go up some if the BUN rises You cannot go too far in lightening up treatment for if you completely discontinue treatment you are back to where you started You have to persist to some degree even though the BUN does rise somewhat because the only chance of bringing this patient back to a reasonably benign phase of hypertension is to persist in the therapy We would lighten up treatment only with the thought of going back again as soon as possible and intensifying treatment to lower the blood pressure adequately

Dr Corcoran You placed considerable emphasis on blood urea nitrogen in patients getting chlorothiazide and so did Dr Hollander As a sort of misplaced renal physiologist I always try to think of blood urea nitrogen as a function of glomerular filtration rate and protein metabolism In patients taking chlorothiazide we have rather firm impressions that the blood urea nitrogen does not mirror changes in glomerular filtration It does mirror changes in glomerular filtration rate in the patients whose glomerular filtration rate has been altered by a ganglion blocking agent There are reports of people with liver disease who have been given chlorothiazide and have demonstrated ammonia intoxication and the thought comes to mind that maybe chlorothiazide could possibly stimulate the renal glutaminase or something like that in ammonia production and thus in the patient with a normal liver contribute to an increase in urea which does not have the normal interpretation of being a function of glomerular filtration rate Your variation in ganglion blocker dosage here is partly predicated on the concept that you are varying dosage not only with blood pressure but also with glomerular filtration rate This is not possible though when the patient is getting chlorothiazide too

Dr Freis I certainly agree with you that chlorothiazide has no particular effect on the glomerular filtration rate in the clearance studies that we have done with the drug We have seen rather marked elevations of blood urea

nitrogen but regardless of the cause this bothers me sufficiently to make me lighten up treatment when that occurs

DR HOLLANDER Did I hear correctly that chlorothiazide in the studies that you have performed does not reduce the glomerular filtration rate? As you know it has been reported by Crosly and others that this compound like Diamox reduces the glomerular filtration rate This reduction of GFR is not necessarily related to a reduction of blood pressure

DR FREIS The clearances that we have done did not show any particular trend or change in any direction

DR CORCORAN Those that we have done have shown a decrease a rather systematic decrease in filtration rate but the increase in blood urea was disproportional I would say a 15 or 20 per cent decrease in filtration rate and perhaps a doubling of blood urea In other words blood urea nitrogen rises more than filtration rate falls That should not happen

DR HOLLANDER Were your glomerular filtration rates reduced to begin with?

DR CORCORAN No not uniformly at all Perhaps in a few of the patients they were

DR HOLLANDER The reason I asked you about that is that the blood urea nitrogen is a rough index of glomerular filtration rate and the blood urea nitrogen does not rise to above normal levels until the glomerular filtration rate is reduced to two thirds of normal at least There would have to be about a 33 per cent reduction in the GFR before this is reflected in an abnormal blood urea nitrogen Perhaps if you began your studies with markedly reduced glomerular filtration rates say in the neighborhood of 40 cc per minute a small change in glomerular filtration rate which might not be detected with the present methods might cause a marked rise in the blood urea nitrogen

DR CORCORAN The other factors are protein breakdown amino acid breakdown and availability of extra ammonia The blood ureas of the Eskimos of the Canadian eastern Arctic average 40 or 45 milligrams per cent and extend up to 60 but they are chewing a lot of meat and that explains it I think

DR MOYER I am a little surprised to see us starting out on intramuscular reserpine in this group of patients usually not considered to be in an emergency state Is this a usual approach?

DR FREIS If the diastolic is below 140 mm Hg begin with oral rather than parenteral reserpine

DR MOYER If there is no evidence of encephalopathy acute heart failure or any other evidence of a real emergency state do the rest of the panel members consider this of adequate urgency to require parenteral reserpine?

Dr Corcoran We use it more or less as a test to see whether we should continue reserpine

Dr Freis You mean parenteral reserpine to test for predicting responsiveness to oral reserpine? You think that the two are comparable?

Dr Corcoran I don t know

Dr Freis I don t think so

Dr Grollman I should think you are not giving it so much as an emergency measure Dr Moyer but rather to elicit a different effect I think the effect after parenteral administration is different than after oral administration—an argument that we had the other day

Dr Moyer You would use it also Dr Grollman?

Dr Grollman Not because of an emergency but in order to elicit a greater peripheral effect which would not be obtainable by the oral route in smaller doses

Dr Moyer In other words you use it parenterally because of greater potency

Dr Grollman That s right

Dr Moyer How about you Dr Meilman and Dr Ford?

Dr Meilman I think that the advantage of giving it by injection is that you get an effect quickly I ordinarily wouldn t feel so impelled to use it by injection in a patient without encephalopathy

Dr Ford I think it is just a matter of saving time I had not thought about doing it but certainly it does save time

Dr Gifford Unless an emergency exists in the form of encephalopathy or acute ventricular failure I don t ordinarily start with intramuscular reserpine

Dr Moyer Dr Smithwick would you outline how you would approach the treatment of hypertension in relation to the medical program? I would gather that you would more or less limit your surgical approach to the latter more severe group of patients

Dr Smithwick I would certainly agree that patients with hypertension who are unresponsive or unreliable or uncooperative or to put it in another way who cannot or will not follow a medical regimen certainly should be seriously considered as candidates for sympathectomy Dr Freis (Table 1) has put down age 45 as the upper age limit for sympathectomy The vast majority of patients who would be operated on would be under 50 certainly I do not think I would necessarily put age 45 as the upper age I would say 50 or less with an occasional patient in the 50 or 55 year age bracket I am very much impressed with the people whom we operated on when they were in their 20's and 30s whom we have now been following for 10 to 20

years who had really severe hypertension with cardiovascular changes of consequence They have been managed very satisfactorily over many years with sympathectomy alone in some instances and combined with dietary restriction a low sodium diet in others In recent years very small doses of the various hypotensive drugs have been used I think that sympathectomy should be considered especially in young females with hypertension of con sequence who desire children and also in young males in their 20s and 30s even though you can handle them medically Nobody knows whether drug therapy will be safe Some of this drug therapy may prove to be safe and entirely satisfactory but my experience goes on up to 20 years We are talking here about drugs that have been available for a comparatively short period of time We are not absolutely certain whether you can continue to give these people what seems to me to be tremendous doses of multiple drugs There may be untoward effects of these drugs that are going to come into being after the people have been taking them for 5 10 or 15 years I believe that we ought to consider operating on these young really severe hypertensives in their 20s and 30s and then add a much more conservative medical program if necessary I think they require far less frequent check ups and their side effects from the small amount of drug that the majority of them have to take are insignificant They have much more freedom for travel or work and so forth so that I think sympathectomy ought to be seriously considered in that group

Dr Moyer This is as you pointed out yesterday a limited sympathec tomy

Dr Smithwick Yes I d say the most conservative type of sympathectomy which doesn t interfere with ejaculation There are rarely serious side effects to it

Dr Moyer Dr Howard would you care to elaborate on that in any way?

Dr Howard My only contribution might be to suggest that more and more of the decisions about the young people be made on the basis of hos pitalized patients because I believe that more and more we will be studying the renal artery before we decide on drug therapy or on sympathectomy in the younger patients I wonder if it isn t a hospital decision in the young patients

Dr Moyer Dr Hollander do you want to express an opinion?

Dr Hollander What I have to say is based on personal observation of the procedure of sympathectomy If I were a hypertensive especially with early signs of vascular disease and my blood pressure did not respond to antihypertensive drugs or I could not tolerate antihypertensive drugs well I would have a splanchnicectomy If I were a young person in my twenties or early thirties and if my blood pressure was not reduced to normal with antihypertensive drugs or if I could not tolerate them especially being a male I would also have a sympathectomy I would have a sympathectomy because the procedure does lower blood pressure If it did not lower my blood pressure I would know that the procedure would make my blood pressure more responsive to antihypertensive drugs In observing the effects

of antihypertensive drugs in sympathectomized patients I am most impressed especially with chlorothiazide We have been most impressed that patients who have been sympathectomized usually get a striking response to very small doses of chlorothiazide in the neighborhood of 62 5 mg to 125 mg a day and this is not a lot of the drug

DR GIFFORD I can say that we rarely and I mean rarely resort to sympathectomy Perhaps that is good perhaps it is bad but unless we have some long term follow ups on patients on drug therapy we are not going to be able to compare favorably or unfavorably with Dr Smithwick s excellent series

DR FINNERTY There is also a difference in regard to the surgeon who does the sympathectomy

DR MOSER We have not done a sympathectomy in six years That is not to say that if we found a young severe hypertensive who did not respond or who had any of the other indications we would not advise it Practically all of our patients respond to drug therapy and those who do not the surgeons consider inoperable or poor operative risks

DR MOYER So you think that most if not all patients are responsive to medical therapy?

DR PERRY We rarely do sympathectomies but I would agree with Dr Smithwick s criteria

DR MEILMAN Do I understand that the operation you are talking about is just a splanchnicectomy? In other words you don t go below the diaphragm?

DR SMITHWICK I think that in the vast majority of patients the type of sympathectomy is a little more extensive than that which Peet originally recommended that is thoracic 8 to 12 You have to go below the diaphragm because I think that you really ought to inspect the adrenals and the kidneys and the renal artery in every patient on whom you operate I think that in the vast majority of patients the lower point of the resection can stop just below the twelfth thoracic ganglion Then you have very very little in the way of untoward side effects and should you want to use a drug later you don t have the problem that you have if they have had an extensive sympathectomy after which the addition of drugs immediately gets you into trouble with postural hypotension I would say in general that removal of 8 through 12 of the sympathetic trunks plus the splanchnics is sufficient

DR GROLLMAN I would be in general agreement with Dr Smithwick s outline

DR DONALDSON I think we are all in agreement that there is a small and selected group that certainly should have the benefit of sympathectomy but for the most part we go along with medical therapy which is extremely encouraging at this time

DR CORCORAN Our experience with sympathectomized people receiving

chlorothiazide is very impressive and although we have rarely recom mended sympathectomy in recent years I suspect that we are going to return to it

Dr Moyer I would like to ask Dr Daeschner if there is anything that he cares to bring out here that he did not bring out in his discussion yesterday

Dr Daeschner My remarks have entirely to do with the problem of hypertension in children There has been a great deal of discussion here concerning the use of chlorothiazide Our limited experience has been that in acute renal diseases as well as chronic renal diseases of childhood chloro thiazide has not been particularly effective in reducing blood pressure It has produced rather marked hypokalemia and alkalosis Reserpine on the other hand has been rather consistently effective Maybe we have been somewhat negligent in not pursuing the study of other compounds in this respect but the results have been so good that we have had little reason to pursue others

When reserpine is not adequate the addition of hydralazine has taken care of the few patients who were not taken care of in other respects In the patients with chronic nephritis and hypertension it has been our experience that a good many of them have much better glomerular filtration rates and renal plasma flows than we would expect from the degree of elevation of blood pressure In some patients the renal biopsy has looked better than we would have anticipated In these patients the careful use of reserpine or hydralazine plus the blocking agents has produced fairly striking results

TREATMENT OF HYPERTENSIVE EMERGENCIES

Dr Moyer Before closing this symposium we should consider the treat ment of hypertensive emergencies again Because of time limitations rather than a general panel discussion I shall summarize briefly certain aspects of the therapy of hypertensive emergencies A short outline that we have used for the treatment of the more common hypertensive emergencies is recorded in Table 5 (See also pages 615 to 640)

Hypertensive crisis and encephalopathy may occur not only in essential hypertension but also in a particular condition such as toxemia of pregnancy or acute glomerulonephritis Before treatment is instituted renal compensa tion should be appraised particularly if cerebration is abnormal The best estimate of renal functional capacity is gained by repeated blood urea nitro gen determinations If this level is normal renal failure is not responsible for any sensorial disturbance

Retinal examination is also essential since severity of retinal hemor rhage indicates the degree of generalized arteriolar damage In addition papilledema is suggestive of increased intracranial pressure and cerebral edema with resultant deranged cerebral function in patients without renal failure

Reserpine

Reserpine* is the preferable drug to be used initially for hypertensive crises or encephalopathy when a delay of two to three hours in pressure

* Rescinnamine (Moderil) in a dose 1 5 times greater than that recommended for reserpine is an acceptable substitute

TABLE 5 OUTLINE FOR ANTIHYPERTENSIVE TREATMENT OF HYPERTENSIVE EMERGENCIES

By John H. Moyer, M.D.

	Initial Therapy					
Emergency	Drug	Dose	Route	Frequency	Adjunctive Therapy When Initial Drug Inadequate	Maintenance Therapy After Emergency Over
Encephalopathy	Reserpine or rescinnamine	2.5 to 10 mg 5 to 15 mg	I.M. I.M.	4–12 hours 4–12 hours	Hexamethonium 10–100 mg I.M. If inadequate then Veriloid titration by I.V. infusion	Chlorothiazide + Rauwolfia + ganglionic blocking agent
Fulminating heart failure	Hexamethonium or Arfonad	10 to 100 mg Titration	I.M. I.V.	30 min to 4 hours Continuous infusion	Reserpine I.M. or Veriloid titration by I.V. infusion	Chlorothiazide + Rauwolfia + ganglionic blocking agent
Intractable angina with severe hypertension	Hexamethonium	10 to 100 mg	I.M.	1–4 hours	Reserpine 2.5 to 10 mg given I.M.	Chlorothiazide + Rauwolfia + ganglionic blocking agent
Hypertensive crisis	Reserpine or rescinnamine	2.5 to 10 mg 5 to 15 mg	I.M. I.M.	4–12 hours 4–12 hours	Hexamethonium 10–100 mg I.M. If inadequate response then Veriloid by I.V. infusion	Chlorothiazide + Rauwolfia + ganglionic blocking agent

reduction is possible If within this time response to initial dosage of 2 5 mg is inadequate an additional 2 5 mg is given and 5 mg doses thereafter as needed As much as 10 mg per dose may be given Usually however dosages in excess of 5 mg do not produce an additional effect No more than 30 mg should be given in 24 hours Prolonged daily administration of more than 10 mg depresses cerebration and may cause a Parkinson like syndrome but these manifestations disappear several days after discontinuation

Ganglionic Blocking Agents

Blood pressure response to ganglionic blocking drugs is most pronounced while the patient is standing Thus they are of limited value in bedfast patients and are used only when the response to reserpine is inadequate or

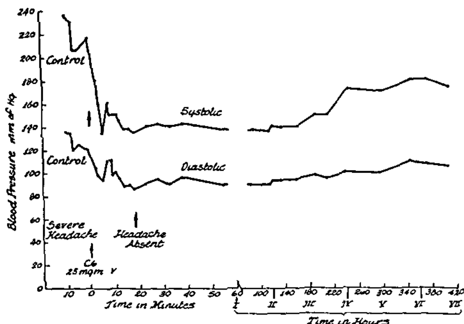


Fig 1 Note prompt fall in blood pressure after administration of 25 mg of hexa methonium intravenously to a patient with severe hypertension

when an immediate effect on blood pressure is mandatory Greater reduction in blood pressure is obtained if 10 to 12 inch blocks are placed under the head of the bed If large doses of these agents cause pronounced orthostatic hypotension careful attention must be given to the degree of pressure reduc tion when the patient is in the tilted position otherwise cerebral ischemia and anoxia may result Also large doses may produce ileus Cathartics should be used freely for relief of constipation Cholinergic agents are sometimes even more effective Prostigmin 15 to 45 mg or pilocarpine 5 to 10 mg before a meal is usually adequate In a comatose patient 1 mg of Prostig min is given intramuscularly For relief of ileus 1 mg should be given every hour until the ileus is relieved

When the response to reserpine is inadequate or immediate pressure reduction is required hexamethonium (Bistrium) 10 mg should be given parenterally (Fig 1) If reduction is inadequate in an hour the next dose

should be 20 mg and subsequent doses are increased or decreased according to the pressure response The pressure should be recorded every few minutes for a half hour after injection since some patients are sensitive to small doses Such careful supervision is not necessary once effective dosage is determined Tolerance usually requires increasing dosages Amounts greater than 75 mg rarely reduce pressure further but rather increase the severity of the side effects

In hypertensive emergencies 100 to 500 mg of hexamethonium in 1000 cc of 5 per cent glucose in distilled water may be infused at a moderate rate until the pressure begins to fall, after which the rate is readjusted Blood pressure and pulse rate should be determined every five minutes Continuous monitoring of the blood pressure is recommended

Pentolinium (Ansolysen) is used in essentially the same manner as hexamethonium For continuous intravenous infusion 50 to 200 mg in 1000 cc of 5 per cent glucose solution is infused at a rate adjusted to the blood pressure response For intramuscular injection an initial dose of 5 mg is used and usually another 10 mg is given in one or two hours Subsequent doses are progressively increased until reduction is adequate or a maximum dose of 50 mg is being given Response is rarely greater with larger doses Should excessive reduction in blood pressure occur any of the effective vasopressor agents will readily correct this problem

Ganglionic blocking agents are particularly useful in severe and acute heart failure (Table 5) in which pressure elevation is sudden As therapeutic blockade is established venous tone is reduced with resultant decrease in venous pressure decrease in right atrial pressure and increase in cardiac output Relief of pulmonary edema is often dramatic Drugs can be given in concentrated solution to avoid extra fluid administration by vein An initial dose of 25 mg of hexamethonium or of 10 mg of pentolinium in 10 cc of fluid is injected slowly with repeated pressure determinations in the opposite arm to avoid overdosage This dose can be increased and repeated after 30 minutes or can be given as often as needed to reduce pressure For maintenance therapy hexamethonium is usually given intramuscularly every two to four hours or pentolinium by the same route every six to eight hours

Trimethaphan camphorsulfonate (Arfonad) reduces arterial blood pressure more rapidly than other ganglionic blocking agents Its effect is transient so that degree of blockade and therefore pressure reduction can be regulated instantaneously However it must be given as a continuous intravenous infusion

Veratrum Drugs

Veratrum extracts are the most potent antihypertensive agents available and are as effective in the supine as in the upright position However because of associated nausea and vomiting and the difficulty of pressure regulation these drugs should be used only when simpler methods of treatment are not successful

Alkavervir (Veriloid) can be given intramuscularly or by continuous intravenous infusion with onset of action in several minutes (Fig 2) Excessive pressure reduction must be avoided In one of my studies nausea and vomiting occurred in seven of 17 patients Nevertheless encephalopathic manifestations abated in all but four patients In seven of 17 patients all

such manifestations were absent as long as pressure reduction was maintained

For intravenous administration an initial priming dose of alkavervir 0 5 microgram per kilogram of body weight per minute is given during a 20 minute period It is prepared by dilution of 10 micrograms per kilogram of body weight of intravenous solution of alkavervir in 20 cc of 5 per cent glucose in distilled water The initial dose may be repeated at least in part Blood pressure should be measured every minute until adequate pressure reduction is obtained then a sustaining solution of 4 mg of alkavervir in 1 liter of 5 per cent glucose in distilled water is given at a rate to maintain



Fig 2 Administration of alkavervir at an initial rate of 0 5 mcg /kg /min produced a harp decrease on blood pressure The desired response was then maintained by doses of 0 07 to 0 06 mcg /kg /min

the desired pressure Blood pressure and pulse rate should be recorded every two to three minutes for the first 30 minutes every five minutes until the pressure is stabilized and then every 15 to 20 minutes until the infusion is complete As soon as feasible oral or intramuscular administration is substituted The first intramuscular injection of alkavervir 0 6 mg is increased by 0 2 mg per dose every four to six hours until significant pressure reduction occurs then more gradually usually in 0 1 mg increments until the desired level is attained When proper dosage is determined frequency of administration is dependent on the length of the time the pressure remains reduced Blood pressure should be recorded at least every 15 minutes until dosage is adjusted Atropine 1 mg can be given for excessive bradycardia

TABLE 6 TREATMENT OF HYPERTENSIVE EMERGENCIES
By WILLIAM HOLLANDER M D

EMERGENCY		DRUGS USED SEQUENTIALLY WHEN PREVIOUS DRUG NOT ADEQUATE
Cerebral hemorrhage	1	Parenteral reserpine 2 5 to 10 mg I M (titration)
	2	Parenteral Arfonad or parenteral Veratrum
Hypertensive encephalopathy	1	Parenteral reserpine
	2	Ganglionic blockers or Veratrum
Acute pulmonary edema (congestive failure)	1	Parenteral digitalis
	2	Parenteral hexamethonium or Arfonad
	3	Parenteral mercurials or chlorothiazide
	4	Parenteral reserpine

but unfortunately there is no effective antidote for related nausea and vomiting

Protoveratrine (Veralba) 0 2 mg/cc is probably as effective as alkavervir The priming dose 0 5 cc in 10 cc of 5 per cent glucose or saline solution is injected intravenously at a rate of 0 5 cc per minute and repeated if necessary When the desired pressure decrease occurs a continuous infusion of 2 mg of the drug in 1000 cc of glucose solution is given at a rate to maintain the desired blood pressure level without causing vomiting usually 10 to 20 drops per minute After the immediate emergency protoveratrine 0 6 cc may be administered intramuscularly Maximum effect occurs in one to two hours and depending on the patient s response dosage is increased or decreased by 0 2 cc every four to six hours Blood pressure should be determined every 15 minutes throughout administration

Maintenance Therapy

After the hypertensive emergency a permanent therapeutic program should be initiated Chlorothiazide 500 to 1000 mg every 12 hours administered indefinitely enhances effectiveness of the primary drugs For long term therapy orally administered Rauwolfia and if necessary hydralazine or a ganglionic blocking agent is usually most effective in severe hypertension When an orally administered drug is substituted for parenterally

TABLE 7 TREATMENT OF HYPERTENSIVE EMERGENCIES
By RALPH FORD M D

DRUG AND ROUTE	
A	Reserpine 2 5 mg intramuscularly every 4 to 12 hours
B	If no response in 12 hours and BUN is less than 40 mg per cent continue reserpine parenterally and give mecamylamine 2 5 to 10 mg orally or intramuscularly every 4 to 12 hours
C	If inadequate respon e within 12 hours and clinical condition is deteriorating continue reserpine intramuscularly and add Veratrum (Vertloid) intravenously at a rate dependent upon blood pressure reduction
	Have norepinephrine infusion on hand for acute hypotensive responses
	Intravenous hydrochlorothiazide may be an additional augmentative agent of value in stage A

administered reserpine 1 mg of reserpine 250 mg of the whole root (Raudixin) or 4 mg of alseroxylon (Rauwiloid) is usually given. After several months this amount is decreased until the smallest effective dose is being employed. Dosage of a blocking agent should be adjusted according to the level of the blood pressure measured while the patient is standing. Therefore the patient should be ambulatory before oral dosage is adjusted.

The treatment programs used by Drs. Hollander, Ford and Gifford are outlined in Tables 6, 7 and 8 respectively. Their approach is generally similar to that which I have just described.

Dr. Perry, do you have any comments?

DR. PERRY: I cannot really give a standardized approach to the treatment of a hypertensive emergency. The best I can do is to say that for a patient whose blood pressure must be lowered as soon as possible we use an intramuscular blocking agent beginning with very small doses since patients who need blockade the most are likely to be the most sensitive. With pentolinium the starting dose we use is 0.1 mg. Assuming that there is not enough cardiac

TABLE 8 TREATMENT OF HYPERTENSIVE EMERGENCIES
By RAY GIFFORD, M.D.

IMMEDIATE	SUBSEQUENT	RESISTANT CASES
Reserpine	Reserpine	
(5.0 mg I.M.) →	(5.0 to 10 mg I.M.)	
with or without	↓↑	
Hexamethonium →	Hexamethonium →	Alkavervir
(15 mg I.M.)	(15 to 100 mg I.M.)	(2.0 mg/20 cc I.V.)
	or	or
	(250 to 1000 mg/1000 cc continuous I.V. drip)	→ Sodium nitroprusside (60 mg/L by continuous I.V.)

failure to retard absorption markedly we successively double the dose at ten to fifteen minute intervals until we have the desired effect. Injections are ordinarily given into the deltoid sufficiently low so that a tourniquet could be placed above it if the need arose. Once the pressure is down it is an individual matter as to how much drug is required to keep it there. We prefer the intramuscular route to the intravenous route because the tremendous individual variation in sensitivity to ganglionic blocking agents makes it very difficult to decide the concentration to put into fluids.

Control of Increased Blood Pressure Associated with Toxemia of Pregnancy

DR. MOYER: Table 9 summarizes the therapeutic outline suggested by Dr. Finnerty for controlling the hypertension associated with toxemia of pregnancy. A detailed description of his approach to the treatment of toxemia is available on page 622.

The procedure as outlined in Table 10 is recommended by Drs. Lindley, Rogers and Moyer for hospitalized patients with toxemia.

Reserpine alone or combined with hydralazine should be given parenterally in the dosages shown in Table 10. In severe hypertension best results

TABLE 6 TREATMENT OF HYPERTENSIVE EMERGENCIES

By WILLIAM HOLLANDER M D

EMERGENCY	DRUGS USED SEQUENTIALLY WHEN PREVIOUS DRUG NOT ADEQUATE
Cerebral hemorrhage	1 Parenteral reserpine 2 5 to 10 mg I M (titration) 2 Parenteral Arfonad or parenteral Veratrum
Hypertensive encephalopathy	1 Parenteral reserpine 2 Ganglionic blockers or Veratrum
Acute pulmonary edema (congestive failure)	1 Parenteral digitalis 2 Parenteral hexamethonium or Arfonad 3 Parenteral mercurials or chlorothiazide 4 Parenteral reserpine

but unfortunately there is no effective antidote for related nausea and vomiting

Protoveratrine (Veralba) 0 2 mg /cc is probably as effective as alka vervir The priming dose 0 5 cc in 10 cc of 5 per cent glucose or saline solution is injected intravenously at a rate of 0 5 cc per minute and re peated if necessary When the desired pressure decrease occurs a continuous infusion of 2 mg of the drug in 1000 cc of glucose solution is given at a rate to maintain the desired blood pressure level without causing vomiting usually 10 to 20 drops per minute After the immediate emergency proto veratrine 0 6 cc may be administered intramuscularly Maximum effect occurs in one to two hours and depending on the patient s response dosage is increased or decreased by 0 2 cc every four to six hours Blood pressure should be determined every 15 minutes throughout administration

Maintenance Therapy

After the hypertensive emergency a permanent therapeutic program should be initiated Chlorothiazide 500 to 1000 mg every 12 hours admin istered indefinitely enhances effectiveness of the primary drugs For long term therapy orally administered Rauwolfia and if necessary hydralazine or a ganglionic blocking agent is usually most effective in severe hyper tension When an orally administered drug is substituted for parenterally

TABLE 7 TREATMENT OF HYPERTENSIVE EMERGENCIES

By RALPH FORD M D

	DRUG AND ROUTE
A	Reserpine 2 5 mg intramuscularly every 4 to 12 hours
B	If no response in 12 hours and BUN is less than 40 mg per cent continue reserpine parenterally and give mecamylamine 2 5 to 10 mg orally or intramuscularly every 4 to 12 hours
C	If inadequate response within 12 hours and clinical condition is deteriorating con tinue reserpine intramuscularly and add Veratrum (Veriloid) intravenously at a rate dependent upon blood pressure reduction
	Have norepinephrine infusion on hand for acute hypotensive responses
	Intravenous hydrochlorothiazide may be an additional augmentative agent of value in stage A

TABLE 10 ANTIHYPERTENSIVE THERAPY IN TOXEMIA PATIENT CONFINED TO HOSPITAL

By John Lindley, M.D., Stanley Rogers, M.D., and John H. Moyer, M.D.

SEVERITY OF DISEASE	RESERPINE	HYDRALAZINE
Mild pre-eclampsia (blood pressure 140/90 to 160/100 mm Hg)	5 mg I.M. or I.V. may be repeated in 1–2 hours if patient still hypertensive. Thereafter 5 mg every 4–6 hours as needed to maintain B.P. below 140/90	*Given only* when normotensive response not obtained with reserpine alone. 5–10 mg may be given as *injection or* 25 *mg in* liter of 10% dextrose in water as slow I.V. infusion
Severe pre-eclampsia	10 mg I.M. or I.V. *may* be repeated in 1–2 hours if patient still hypertensive. Thereafter 5 mg every 4–6 *hours as needed to* maintain blood pressure below 140/90	10 to 20 mg I.V. as single injection for rapid initial blood pressure reduction if desired response not obtained from reserpine; repeated only when normotensive state not maintained with reserpine alone. Fifty mg in 1 liter of 10% dextrose in water may be given by continuous I.V. infusion when blood pressure is labile or when it is difficult to get desired response
Severe pre-eclampsia and primary hypertensive disease (blood pressure 160/100 mm Hg)	Same as for severe pre-eclampsia	Same as for severe pre-eclampsia
Eclampsia	10 mg I.V. may be repeated in 1–2 hours if patient still hypertensive. *Thereafter* maintenance dose of 5–10 mg every 4–6 hours to insure sedation and normotensive state	If B.P. 170/100 or above, 20 mg as single I.V. injection. If B.P. between 150/90 and 170/100, 10 mg as single I.V. *injection. If B.P. between* 130/80 and 150/90, 25 mg in 1 liter of 10% dextrose in water given slowly as continuous I.V. *infusion so* that it may be discontinued quickly if B.P. falls too low. If after the initial injection hypertension is *labile or* difficult to control, 50 mg in 1 liter of 10% dextrose in water should be given as continuous I.V. infusion

Sulfamerazine Therapy For dosage and routes of administration, see chart LXVI on page 1040

Correction of Dehydration Dehydration should be corrected by administering 3,500 c c of normal saline, with or without a 5 per cent solution of dextrose A daily intake of 3,000 c c is recommended to ensure an adequate urinary output

Administration of Antiserum It appears likely that with the ever growing use and availability of penicillin antiserums will play a diminishing role in the future management of meningitis The value of these serums is questionable and the committee representing the Office of the Surgeon General (19) does not recommend the use of antisera, even in the treatment of meningococcic meningitis If penicillin is not available, and if there has been no response to chemotherapy after forty eight hours of treatment, antisera may be tried

Anti meningococcus Serum This is recommended for patients who fail to improve sufficiently after 24 to 48 hours of chemotherapy or earlier, and in cases of fulminating or severe disease About 50 to 100 c c should be given intravenously as the initial dose to an adult of average weight, further doses depend upon the initial response Intraspinal administration is no longer commonly practiced

Anti pneumococcus Serum Therapy is begun for the patient as soon as the causative organism has been determined, and particularly for those who do not respond favorably after chemotherapy has been tried for 24 or *48 hours The intravenous route is used* 200,000 units usually suffice for an initial dose Intrathecal administration of serum with complement is recommended by Leyshon (21)

Anti influenza bacillus Serum The intravenous route is used for all type B infections The initial dose consists of unconcentrated rabbit antiserum *1 0 to 2 5 c c per kg of* body weight, or the equivalent of 50 to 100 mg of antibody nitrogen depending upon the severity of the infection Intrathecal injections of antiserum with complement are advised by some clinicians for those patients who fail to respond within 48 hours after intravenous sero therapy has been started

When to Change or Discontinue Sulfonamide Therapy When the sulfonamide derivatives are being used in the management of meningitis *change the dosage of the drug* if the following drug blood levels are not maintained

a) Sulfadiazine—10 to 15 mg per 100 c c of blood
b) Sulfamerazine—10 to 12 mg per 100 c c of blood

Change to another sulfonamide derivative under the following conditions

a) *In the event of a marked toxic reaction,* e g acute hemolytic anemia marked leucopenia, jaundice dermatitis or fever
b) Greater susceptibility of the causative organism to a compound other than the one originally administered Change to sulfathiazole or sulfadiazine for infections caused by staphylococcus or colon bacillus, to sulfadiazine for infections caused by the Friedländer bacillus
c) *In the event of a poor response to adequate doses* associated with a high concentration of the compound in the blood

Continue therapy after complete clinical and bacteriologic recovery from the following meningitides for the approximate periods suggested

Meningococcic meningitis—2 to 5 days
Pneumococcic meningitis—7 to 14 days
Streptococcic meningitis—7 to 14 days
Staphylococcic meningitis—2 to 3 weeks
Influenza bacillus meningitis—2 or 3 weeks
Other organisms—1 to 3 weeks depending upon the speed and completeness of recovery

Chemotherapy should be discontinued temporarily or the dosage reduced and the fluid intake increased if there is gross hematuria, *oliguria anuria or if the blood shows an excessively* high concentration of the drug or of non protein nitrogen In the event of the above complications sodium bicarbonate should be given orally or a sixth molar solution of sodium lactate, intravenously

Laboratory Aids in the Control of Treatment *When it is possible* the level of the drug in the blood or the spinal fluid or in both should be determined every day until the infection has cleared up and, thereafter every third day It is well to determine the hemoglobin and red cell count two or three times each week A white blood cell count should be made every *two or three days during the course of the* sulfonamide treatment A differential count should also be made daily if the total leucocyte is below normal or if the treatment has lasted

for more than twelve days The urine should be examined daily for crystals and red blood cells The morning specimen is the best for this purpose Neglect to do this invites trouble for blockage of the ureters may occur In the event of hematuria or anuria developing a daily non protein nitrogen determination should be made

In patients with persistent fever, blood cultures should be repeated at two or three day intervals, particularly, if the initial culture is positive Continued bacteremia in the presence of a clearing meningeal infection strongly suggests the presence of endocarditis or a focus of infection elsewhere

Rundlett (20) in 23 cases found that a rise in the cerebrospinal fluid sugar is a favorable sign and usually precedes cytologic or clinical improvement He believes that the level of the spinal fluid sugar gives rapid indirect evidence of the bacteriological nature of the spinal fluid more accurately than the smear, culture or cell count

Treatment of Focal Infection Surgical intervention when indicated is usually undertaken after a minimum of from 12 to 24 hours of adequate chemotherapy When there is any doubt operation should be performed Pus which is accessible should be evacuated immediately

Supportive Treatment In general this includes competent nursing care as in other severe infections For sedation one may use the *barbiturates, chloral hydrate* or *paraldehyde* In the event of anemia a blood transfusion should be given Should agranulocytosis or marked granulocytopenia develop *pentnucleotide, crude liver extract* and *blood transfusions* are recommended A convalescent period of at least one month should follow clinical recovery

Management of a Relapse or Recurrence In the event of a relapse one should consider in the differential diagnosis drug fever, serum sickness and infection with the original organism or with a different one either at the same focus or at another site A lumbar puncture and complete blood studies should be made and treatment resumed as described for the original infection

The Treatment of Tuberculous Meningitis

Tuberculous meningitis does not respond to treatment The general management is symptomatic *Codeine* and *salicylates* may be necessary to relieve the pain and *chloral* to control convulsions In a recent issue of the Staff Proceedings of the Mayo Clinic it is stated that one case was cured by the use of *promin*

The Treatment of Syphilitic Meningitis

Moore (22) recommends arsphenamine as the best drug for the treatment of early meningeal syphilis the initial dose is from 0 3 to 0 4 gm rapidly increased to a maximum of 0 6 gm For immediate symptomatic effect he gives 0 4 gm every 4 to 5 days for twelve injections combined with from 6 to 20 grams daily of potassium iodide The improvement is said to be dramatic Further treatment by the intensified routine treatment (see page 408) *brings about serologic reversals in from 60 to* 80 per cent of cases If serologic reversal is not obtained after a year of such treatment, Moore advises tryparsamide if improvement does not follow in from 6 to 12 months he advocates fever treatment

For late cases the intensified routine treatment with arsphenamine is advised by Moore who believes that continuance of the intensified routine system of treatment depends not so much on symptomatic relief as on the presence or absence of serologic improvement at the end of six months If then the spinal fluid findings have changed for the better, the treatment is continued for another six months If the fluid is of the paretic type tryparsamide, fever therapy or both are introduced as soon as possible In view of recent investigative work *penicillin* appears to be the drug of choice for this condition

Whooping Cough—Pertussis

Pertussis is an acute highly contagious specific disease caused by the pertussis bacillus of Bordet and Gengou *Hemophilus pertussis*, it is characterized by attacks of spasmodic coughing ending in an inspiratory whoop frequently accompanied by vomiting

SOURCE OF INFECTION

Discharges from the laryngeal and bronchial mucous membranes of infected persons

MODE OF TRANSMISSION

The disease is *transmitted by contact with* an infected person or with articles freshly

soiled with his discharges Some susceptible contacts may fail to develop the full clinical picture and may have an abortive infection during which period they can transmit the disease The *incubation period* is commonly 7 days almost uniformly within 10 days and rarely exceeding 16 days The organisms are present in enormous numbers on the *mucous* membranes and pharynx during the active phase of the disease During the second week, definite specific agglutinins opsinins and complement fixing antibodies against the causative bacilli appear in the patient s blood

COMMUNICABILITY

The disease is particularly communicable in the early catarrhal period before the typical cough confirms the diagnosis After the paroxysms have become established, communicability gradually decreases and becomes negligible for ordinary nonfamilial contact in about three weeks even though the spasmodic cough with a whoop may persist The communicable stage must be considered to extend from 7 days after exposure to an infected individual to 3 weeks after the onset of typical paroxysms

SUSCEPTIBILITY AND IMMUNITY

Susceptibility is general and there is no *natural immunity* The greatest susceptibility is in children between six months and five years of age after which there is some decrease One attack confers a definite and prolonged immunity although second attacks do occur A brief *passive immunity* may be conveyed to young children by convalescent serum or adult whole blood Artificial active immunity is still in the experimental stage, immunity is produced in some but is not perfect Susceptibility is higher in females at all ages than in males and in negroes than in whites Convalescent serum or plasma is the best medium for exposed infants or susceptible children who are debilitated By this method, passive immunity can be obtained by the intramuscular injection of 10 to 20 c c of such serum or plasma There is some evidence that attacks are milder in the vaccinated Sauer vaccine containing 20 billion pertussis organisms per c c is given in divided doses over a period of one month The first dose is 1 0 c c the second given two weeks later is 2 0 c c and four weeks following the initial dose the third dose of 2 0 c c in infants, and 3 0 c c in adults is given This vaccine is never advised before the age of seven months Recently, the intranasal instillation of the soluble antigenic substances of H pertussis organisms has been reported to be effective in bringing about a *cessation or amelioration* of the paroxysmal cough and a decrease in the duration of the disease

The disease occurs among children everywhere regardless of race, climate or geographical location The incidence is lowest in August, September and October The highest mortality is in the first year of life and in the spring months

CLINICAL CHARACTERISTICS

Pertussis is characterized by a typical cough usually lasting from one to two months The initial symptoms are much like an ordinary tracheo bronchitis, 25 per cent of cases do not progress beyond this stage The cough gradually becomes paroxysmal usually within from one to two weeks The paroxysms are characterized by a repeated series of violent coughs, each series consisting of many coughs without intervening inhalation and often followed by the characteristic sonorous inspiratory whoop Paroxysms frequently end with vomiting of a clear tenacious mucus The attack leaves the child exhausted and frequently mentally confused In infants the respiratory embarrassment may be sufficiently severe to require artificial respiration The attacks are more frequent at night and are aggravated by smoke, drafts cold drinks, and in closed rooms The strain of coughing may rupture blood vessels *in the lungs, skin or conjunctive* The leucocyte count is elevated and may reach 15 000 to 30,000, the differential may show 80 to 90 per cent lymphocytes After from one to three weeks the stage of decline appears with coughing without whooping and finally the cough ceases entirely

DIAGNOSIS

The etiologic agent may be recovered by use of cough plates with special media which is allowed to solidify in a Petri dish and is held vertically a few inches in front of the patient s mouth who is permitted to cough directly

onto the plated media In infants, nasopharyngeal swabs may be used instead of plates The plate test is positive in about 80 per cent of cases in the catarrhal and early paroxysmal phase of the disease A negative culture does not rule out pertussis Leucocytosis and lymphocytosis are present A history of exposure and the presence of respiratory symptoms are highly suggestive

TREATMENT

Convalescent serum or *plasma* should be given to contacts babies and debilitated persons It may prevent the development of pertussis, or at least modify the attacks if given early in the incubation period The administration of *Sauer vaccine* early in the disease may likewise have a modifying effect on the attacks It has been giving excellent results as a prophylactic, but has shown little if any effect in the paroxysmal stage The *patient should be isolated in order to protect* others *Rest in bed* is advisable in the catarrhal and paroxysmal stage with sufficient protection from drafts and abrupt temperature changes The cough may be relieved by *sedatives* such as codeine bromides luminal chloral, chloroform or even ether in oil given per rectum Expectoration may be aided by *steam inhalations* In severe cases *suction* or *bronchoscopic aspiration* may be necessary to expel mucus especially when it has caused atelectasis If cyanosis develops *oxygen therapy* is necessary A light easily digested diet is permissable

COMPLICATIONS

Complications are important in pertussis The most common are bronchitis epistaxis and conjunctival hemorrhage, bronchopneumonia otitis media meningitis atelectasis and emphysema hernias and nutritional disturbances Intracranial hemorrhages have been reported Tuberculosis has been activated and tetany may occur as a result of the alkalosis caused by repeated vomiting

CONTROL

Children under three years of age should be protected against contact with any other children with cough and fever of whatever origin and especially if pertussis is suspected or known to be prevalent Isolation of children over two years is impracticable and when the weather permits should not be insisted upon at the expense of fresh air in the open *Quarantine* is limited to the exclusion of non immune children from school and public gatherings for 14 days after their last exposure to a recognized case This applies to exposures in the household or under similar conditions This precaution may be dispensed with if exposed non immune children are observed with care by a physician or nurse on their arrival at school each day for 14 days after their last exposure

Typhoid Fever

Typhoid fever is a general infection due to the typhoid bacillus It is characterized by a continued fever involvement of the lymphoid tissues especially with enlargement and often ulceration of Peyer's patches enlargement *of the spleen usually rose spots on the trunk*, diarrheal disturbance and a variety of severe constitutional symptoms accompanied by parenchymatous involvement of various viscera The liver kidney and heart show degenerative changes The infecting micro-organism can be found in the blood feces and urine

The source of infection with the typhoid bacillus (*Eberthella typhi*) is the feces and urine of infected individuals Healthy *carriers are fairly common The disease is trans*mitted by direct or indirect contact Indirect means of transmission are contaminated water, milk, and shellfish and probably flies Disasters such as earthquakes floods or fires which lay waste large urban areas give rise to epidemics by forcing the population to live in crowded quarters with poor sanitation The usual incubation time is about 14 days but may be as short as 3 or as long as 38 days The disease is communicable from the time of the prodromal symptoms throughout the illness and relapses during convalescence and until repeated bacteriological examination of the discharges show continuous absence of the infecting organism Males and females are equally susceptible and all ages may be attacked but the victims are those usually between the ages of 15 and 25 years The disease is more prevalent from June to December with the highest incidence in October

TABLE XLIX

Differential Diagnosis of Common Diseases Simulating Typhoid Fever

(Modified after Table by Wallace M. Yater)

	Typhoid Fever	Miliary Tuberculosis Typhoid Form	Bacterial Endocarditis	Pyelitis	Undulant Fever	Influenza
Onset	Rarely acute	Insidious	Insidious	Acute or insidious	Moderately insidious	Acute
Fever	Slow rise, high continuous, slow fall	Remittent or intermittent, sometimes higher in the morning than the evening (102-104 F.—99.)	Irregular, not very high in the subacute, septic type in the acute	Irregular and often intermittent	Prolonged and daily remittent. Textbook undulations rarely seen	High at first, falling steadily during next few days
Pulse	Relatively slow and dicrotic	More rapid than warranted by fever present	Rapid	Rapid	Often slow and is proportional to fever	Relatively slow
Respiration	Not remarkable	Rapid	Not remarkable or dyspnea	Not remarkable	*Not remarkable*	*Relatively slow*
Main Symptoms	Malaise, headache, bronchitis, [illegible] delirium, may be diarrhea and abdominal [illegible]. Fever rises steadily step-like in the 1st week, continues high 103-104 F. for 2nd week	Malaise, bronchitis, cyanosis, pulmonary signs, [illegible] evidence of meningitis	Diastolic heart murmur, embolic phenomena, anemia and petechiae, chills and sweats	Chills, pain and tenderness in renal [illegible], frequency and burning on [illegible] in the acute form	[illegible] foul odor to perspiration, chills, weakness, abdominal pains and migratory polyarthritis, backache	Headache, pain in back and limbs, myalgia, ostalgia, prostration and cough
Rash	Roseolar maculopapular, mainly abdominal [illegible] 2nd week	None usually but sometimes rarely present	Petechiae variable and often late	None present	Small pink macules most prominent on the abdomen [illegible] constant	None
Splenomegaly	Almost always but moderate	Fairly often moderate	Common moderate	Not present	In about 50 per cent cases moderate	None
Duration	4 to 5 weeks	2 to 6 weeks. Death follows after increasing prostration and emaciation	Weeks or months but fatal prognosis	7 to 10 days when acute, recurrent for years when chronic	6 weeks to several months	2 to 5 days when uncomplicated
Leucocyte Count	Leucopenia with a relative lymphocytosis	Usually moderate polymorphonuclear leucocytosis, sometimes leucopenia with increase in polymorph	Variable, often a moderate polymorphonuclear leucocytosis	Polymorphonuclear leucocytosis	Normal or leucopenia with relative lymphocytosis	Leucopenia with relative lymphocytosis
Laboratory Diagnosis	Positive results of blood, urine, faeces in 1st week. Widal after 1st wk 1:100 titre to high	X-ray of the chest	Positive blood culture for organisms	Pyuria bacilluria	Normal sed rate. Blood culture with ... method. Spinal fluid culture when C.N.S. involved or guinea pig inoculation with several c.c. of blood from suspected patient. Indirect method: Blood agglutination usually positive from 5 to 14 days after onset. Titre 1:80 is significant but cross agglutination ... in 10 per cent cases. Previous exposure and infection will give positive test. Skin test with Brucella ... 0.1 cc of 1:10 dilution ... mildly ... in 24-48 h	Not specific

	B h p m	Typh F	Rocky M t F r	Mal	T h o s	Syph l
On t	A te	A te w th h ll	Ac t	A t	A ut	I d
F	U ally h gh w th l t ly l ght m o	R p d r th h gh th t em	H gh t f 2 w k w th f ll by ly s n 3 d ek	R g l r o gula fl t t d p d g po th type	R m tt nt a d t m tt t fo d y r w k	L w g le
P l	R r d	P po t lt f e	E	E e	M y b e c s	\ ble
R p t	R p d d ffc lt	R p d	R p d	R p d	Oft n r p d	Not m kabl
M Symp t m	C gh \ th ty p t m e dy p a s b p t t l s g f sol d t	H d he act d l m p tr t d co gh	H d h my lg ost l g p t at d l m d ugh C j t t s d phot ph bia H)p he f k C m s e cas	Ch ll f d t r g l r r g l d p d g p the type	P t ato d h d musc lar h g Dy phag h a se s dem b t yes Em t n a m	H t ry of p ma y o e o d rj le E id n f h p t l me t the s g f sypl l
Ra h	N	M l p s gf mp nk t b w h r d p t ch l the t u k e t m t s b t ot th f e	Ma la pass gf mp k t b w h d th pe t h l ppe s f t o ts m b k p lm l n 3 d 4th 5th d y	N	T s t ca lat n f rm	Mac l p p l l l g mmato w d p l ymmet l l r p g s
Spl megaly	No	Oft t fi t a ly l t mod te	P t ally l ay h t m d ate	F q t m d t ly la g firm	O o lly	O c o lly
Du t n	6 w ks t e ral m th	2 w k	3 w k	S e al w k	2 to 8 w ks	W k mo th
Le yt C t	Mod at h gh polym pho l le cyt	Sl ght l ocyto i	Sl ght l cyt s	L p n w th rc l ge mo a d p e of p gm ted leu o yt	M k d l yt (30 000) th h gh o p a p t 0 p c t)	N mal
L bo t ry D g	\ av of h t Sp t m typ g	P t e W l F l t fte 3 to 4 d y t Pr t \ 19 Al p t t R Mt Sp F v r a im l oc lat n may b ne y	P t e W l F l t ft 3 to 4 d y to P t \ 19	Pl m d bl o l f lm St dy th k me	Stool m at ly b op y l te of m e cut v l e	P s t bl d r p al fl d ll m o oth t t (H to Kl e E gl Ma K lmer)

Some people apparently have an acquired partial immunity. Recovery from typhoid fever usually gives immunity of a permanent nature, but second and third attacks are not rare. Typhoid carriers, especially food handlers, play an important role in the spread of the disease and all food handlers should be *required to undergo examinations periodically*. Carriers of virulent typhoid bacilli have been found who have never had the disease. No universally successful method of managing the carrier question has been attained. It is *important to know that unusual or variant* forms of the typhoid bacilli may cause disease, and laboratory technicians should be aware of their existence so that they will not be discarded as contaminants.

Typhoid fever is widespread throughout the world regardless of age, sex, race, climate, or geography. It was formerly prevalent in most large cities of the United States and in many rural areas both in epidemic and endemic form. It is still endemic in some rural areas of the Southern United States but is now usually seen only as sporadic cases and as small contact and carrier epidemics. It is steadily falling in incidence, particularly in all urban areas supplied with pasteurized milk and where sewage is disposed of without polluting the water supplies, food, or surface of the soil. According to statistics reported deaths from typhoid fever in the United States during 1941 numbered 1,088.

CLINICAL FEATURES

The prodromal symptoms of typhoid fever are malaise, chills, fever, headache, epistaxis, anorexia and myalgia. The onset is usually gradual and is characterized by an intensification of the prodromal symptoms accompanied by cough and perhaps diarrhea or constipation. The fever is continuous and slowly rises in step like fashion to a high plateau where it remains for about two weeks; it then drops in irregular fashion during the next 10 to 14 days. At its peak, it is between 104° and 105°F. About the end of the first week a characteristic eruption appears in the form of irregularly spaced rose spots on the abdomen, chest and back. A careful search may be necessary to find them. They are from 1 to 3 mm in diameter, slightly raised, appear in crops, blanch on pressure and persist for several days. The pulse is typical of typhoid fever. It is dicrotic and slow in relation to the fever. The double pulsation at the radial artery shows no compensatory pause. It usually disappears during the third week. Other findings are a low blood pressure, leucopenia with a relative lymphocytosis and splenomegaly. In 85 per cent of cases the blood culture is positive during the first week of the disease.

During the second week the symptoms are aggravated; the fever continues, the pulse rate *increases*, abdominal distension and tenderness are marked and there may be pea soup stools. There may be delirium. By this time stool and urine cultures are positive and the Widal test shows an increasing titer in the blood. *To be diagnostic the titer should* be at least 1:100. A rising titer is especially significant. Those who have been vaccinated may show a titer of 1:80. Miliary tuberculosis may cause a positive Widal but only in titer up to 1:20.

In mild or moderate cases recovery begins by the third week and is manifested by a subsidence of the fever and the symptoms. In those who have the severe form of typhoid fever there may be signs of intestinal perforation and hemorrhage. The appearance of even a small amount of blood calls for immediate cessation of food. Blood transfusions may be necessary. Perforation is suggested by sudden abdominal pain with rigidity and shock. This emergency calls for immediate surgical intervention. These two complications—perforation and hemorrhage—usually occur in the third week of the disease and in from 1 to 5 per cent of cases. Other complications are cholecystitis, thrombosis of veins *during convalescence*, myocarditis, nephritis, periostitis, spinal arthritis, splenic rupture, pneumonia, psychosis, ulceration of the larynx, otitis media, parotitis and thyroiditis.

In the fourth week convalescence is usually well under way or the case has progressed unfavorably and is near death.

DIAGNOSIS

The diagnosis is made by repeated cultures *of blood*, urine, feces and agglutination tests. The differential diagnosis is discussed on Table XLIX, see page 768.

TREATMENT

There is no specific treatment for typhoid fever The therapy constitutes good nursing supportive and symptomatic therapy preferably in an isolation hospital The local health authorities should be notified in orde that contacts can be vaccinated and the source of infection investigated The patient's bowel and urinary discharges should be disinfected as well as all articles which have come into contact with him Release from isolation should be determined by the recovery of two successive negative stool cultures and urine specimens collected not less than 24 hours apart The diet should be of high caloric value (3000 C) bland, easily assimilated and supplemented by the necessary vitamins It should be of low residue Five or even six feedings daily may be necessary Intravenous fluids such as 5 to 10 per cent glucose in normal saline and blood transfusions when necessary are of value Constipation is treated with mineral oil or enemas Fever is relieved by ice caps or alcohol sponging Diarrhea is controlled by eliminating the fats and sugars and prescribing *paregoric bismuth subnitrate* or *kaolin* Purgatives are not given under any circumstances and cold tubs are not advised The convalescence may be protracted and relapses occasionally occur The patient is permitted out of bed after the temperature has been normal for from ten days to two weeks

Paratyphoid Fever

Paratyphoid fever is a general infection greatly resembling typhoid fever and differentiated from it only by bacteriologic methods It is characterized by a continued fever and the involvement of the lymphoid tissues of the intestines enlargement of the spleen and a variety of constitutional symptoms sometimes rose spots on the trunk and usually diarrheal disturbances The onset is a little more abrupt than typhoid fever is milder and terminates sooner

The *etiological agent* is the paratyphoid bacillus A B or C *Salmonella paratyphi Salmonella schottmulleri* and *Salmonella hirshfeldi* The *incubation period* is from four to ten days the average being seven days The modes of transmission communicability susceptibility and immunity are similar to those of typhoid fever The treatment is also similar to that outlined for typhoid fever

Tetanus

Tetanus is an infectious disease characterized by painful muscular contractions at first of the masseter and neck muscles and later of the muscles of the trunk Rarely the rigidity is confined to the region of the injury

The etiologic agent is the tetanus bacillus *Clostridium tetani* The source of infection is street dust, manure, soil feces and contaminated catgut material Wounds caused by blank cartridges and fireworks or indeed any wound may become infected with the spores of tetanus These spores have the familiar drumstick appearance and are very resistant to sterilization B tetani elaborates one of the most powerful exotoxins known which has an affinity for the central nervous system it usually affects the motor nerves although it sometimes involves the sensory nerves as well The average incubation time is about 5 days

CLINICAL FEATURES

There is usually a history and visible evidence of a recent wound The prodromal symptoms are restlessness, irritability slight rigidity of the neck spasm of the muscles of mastication, difficulty in opening the jaws convulsions opisthotonos and a sardonic smile due to spasm of the facial muscles Any slight noise or stimulus will set the muscles into spasm moderate fever and leucocytosis abdominal rigidity dysphagia, cyanosis, increased spinal fluid pressure with normal cell and globulin values The disease takes a rapid course death usually occurring in 3 or 4 days from asphyxiation caused by spasm of the respiratory muscles or to bronchopneumonia or circulatory failure

Various types of tetanus are described such as traumatic postoperative umbilical (cord infections) and local tetanus which occurs when an inadequate dose of antitoxin is given and is manifested by rigidity of the muscles about the site of the injury Cases which live to nine or ten days have an excellent chance of recovery

TREATMENT

Prophylaxis is most important Passive immunity of short duration can be produced by the injection subcutaneously of 1500 units tetanus antitoxin which should be increased if the wound is severe The wound should be well cleaned but not cauterized since necrotic tissue favors the growth of the tetanus bacilli It is becoming more apparent that passive immunization while of the utmost value is not invariably successful in either preventing the disease or in lessening its severity Recently Cooke and Jones (26) have shown that passive immunity obtained with 1500 units of tetanus antitoxin lasts for about three weeks but if larger amounts are given as for instance 100,000 units immunity can be demonstrated for eleven weeks Active immunity can be produced by the injection of tetanus toxoid and this is the method adopted by the United States Armed Forces Three injections of 1 c c are given at intervals of three to four weeks A booster' dose of 1 c c is given one year after the initial vaccination and also to any who might be exposed to enemy action

After the signs of tetanus have appeared, tetanus antitoxin should be given in sufficient dosage This is considered to be between 30 000 and 100 000 units and some have given as high as 300,000 units in severe cases The antitoxin is usually given intramuscularly, although it can be given intravenously Some inject 5000 units around the wound Intraspinal treatment is not advised

Rest with sedation is very essential for the well being of the patient This is accomplished by strict seclusion in a quiet, darkened room and forbidding visitors There should be no unnecessary handling of the patient such as may be entailed by visits for laboratory work, bathing, shaving dressing of wounds and even feeding or the administration of drugs The reflex excitability is reduced to a minimum with the use of sodium amytal chloral hydrate, or morphine Anesthetics may be required, of these *avertin* has been found to be the most satisfactory It is given in solution per rectum, the initial dose being 25 mg per kilo of body weight and subsequent doses of 10 to 15 mg per kilo at 15 minute intervals until complete relaxation has been induced This can be repeated if necessary every four to six hours for several days During the time the patient is under sedation he can be fed through a stomach tube which obviates his chewing When a developing pneumonia is suspected, a trial course of *sulfadiazine* should be started The drug may be pulverized and given in milk or juices Convulsions may be controlled or diminished by intravenous injections of *magnesium sulfate*, in dosage of 1 c.c of a 25 per cent solution for each 20 pounds of body weight Whatever drugs are used one tries to keep the patient relaxed without complete narcosis and without endangering respiration With this in mind, provision should be made for emergency administration of oxygen or carbon dioxide should either be necessary Surgical measures may be required They depend upon the clinical condition of the patient and upon the nature, extent and location of the injury In local tetanus the mortality is so low that any radical operation is rarely necessary A safe rule is to seek surgical consultation when there is doubt

Anthrax

Anthrax is a rare but historically important disease It is a fatal disease in animals death usually occurring within thirty six hours The *etiologic agent is the anthrax bacillus*, or *Bacillus anthracis* The source of infection is hair, hides, flesh and feces of infected animals The disease is *transmitted* by inoculation as by an accidental wound or scratch inhalation of spores of the infectious agent *ingestion of insufficiently cooked* meat and by flies and mosquitoes The *incubation period* is within 7 and usually less than 4 days The disease is communicable during the febrile stage of the disease and until the lesions have ceased to discharge Infected hair fur or hides even though dried may communicate the disease many months after slaughter of the animals unless disinfected

Immunity may develop following an attack of the disease Artificial active immunity widely used for animals is not appropriate for clinical use The prevalence of anthrax i rare and sporadic in man and associated onl with the disease in cattle or with the handling of hide and hair from infected animals It is seen in epidemic form in cattle in various foreign countries from time to time In the

five year period from 1929 to 1933, 342 cases of human anthrax were reported in the United States During the first World War there were 149 cases of anthrax with 22 deaths all of which were traced to the use of infected shaving brushes

CLINICAL FEATURES

Human anthrax occurs in two forms the external type being caused by direct inoculation through a cut or an abrasion, and the internal, by ingestion or inhalation of the bacilli or their spores The external form comprises about 90 per cent of all cases Following the initial papule and vesicle at the site of inoculation an eschar develops and later a hard edematous swelling of deeper and adjacent tissues The lymphatics are outlined and the lymph nodes become swollen and tender There may be fever, burning and itching, but there is rarely any pain If recovery occurs it is preceded by sloughing of the central portion occupied by the eschar and healing Constitutional symptoms do not run parallel with the gravity of the lesions Internal anthrax resembles intestinal poisoning, toxic pneumonia, or meningitis In the pulmonary form blood cultures are of little help in the diagnosis for they are rarely positive until just before death which in the great majority of cases occurs rapidly and before the disease is even suspected In the gastrointestinal form death usually results within five days

TREATMENT

Surgical treatment should be avoided as it only spreads the infection In a review of 60 cases Gold believes that the administration of *sulfathiazole* is the best treatment (21) In his experience anti serum provokes serum sickness and neoarsphenamine is of little value Recently *penicillin* has been shown to be the drug of choice Reimann believes that the great majority of patients recover without treatment and that the mortality rate is lower than is commonly believed

GENERAL MEASURES

Animals ill with the disease should be isolated immediately and put in the care of a veterinarian Those proved to have the disease should be killed and promptly destroyed preferably by incineration Shipments of hides bristles wool, or hair from sources not known to be free of anthrax infection should be examined by an expert bacteriologist Hair wool hides or bristles etc should be disinfected before they are used or sorted if they are known or suspected to be a source of infection The sale of the hide of an infected animal should be prohibited

Leprosy

Leprosy is a chronic infective granuloma Today leprosy is chiefly confined to the tropics and subtropics It is believed that there are many cases at large in China, Japan India, Russia Australasia, Africa, the Caribbean Islands, Central America and Mexico and tropical parts of South America The endemic centers in the United States are confined to Minnesota and states bordering on the Gulf of Mexico namely Florida, Texas and Louisiana Galveston is the oldest focus of infectivity in Texas In an attempt to link the human infection to murine leprosy 23 000 rats in this region were examined and only 7 were found to be leprous as shown by the detection of acid fast bacilli in tissue smears Leprosy has occurred on the West Coast in California and as an imported disease on the Atlantic seacoast

MODE OF TRANSMISSION

Its mode of transmission is still a subject for study and controversy We cannot go beyond the statement that it is a contact disease There is no substantial foundation for the belief that heredity is a determining factor Close and prolonged family contact is the current view of transmission It has been shown in Hawaii that when children of known lepers are removed from home immediately after birth, the chances of their developing the disease become very remote Climate race and density of population have been eliminated as factors McCoy has stated that with one doubtful exception he has been unable to find any record of anyone having been infected with leprosy in New York City despite the fact that many thousands of foreigners including many Puerto Ricans have been domiciled there

ETIOLOGIC AGENT

While many accept the Hansen bacillus as the etiological agent in leprosy, there is no proof Nor can it be said with certainty that the Hansen bacillus has ever been cultivated on artificial media Direct transmission to man by inoculation of infective material has also failed It has been impossible for any workers to establish by serologic methods the relationship of cultivated organisms to leprosy







Fig 150 Bone Lesions in Leprosy

The *incubation period* is about five years on the average but it may extend to twenty years

The history during this period may reveal little but febrile attacks There is no initial lesion The first symptom may be an exanthem on the hands face arms or legs or it may be manifested by a neuritis This is a disease of great chronicity and is characterized by periods of acute reaction alternating with periods of quiescence which may last for months or years

ing (6) Less frequent symptoms were wrist or foot drop, painful hands shriveled or wrinkled skin swelling of the ears and sore eyes and ears

The cutaneous lesions may assume an exanthematous form and distribution There may be reddish brown or fawn colored patches slightly elevated, they may cause itching or burning These patches are of diagnostic im-

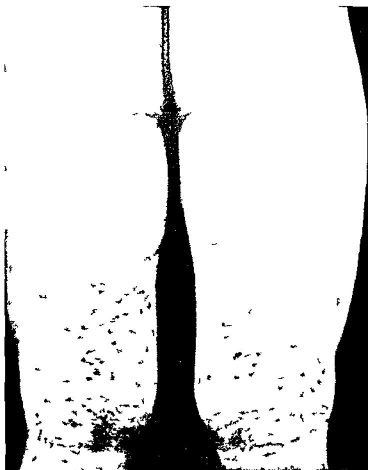


Fig 151 Reddish brown patches diagnosed erythema multiforme until examination demonstrated anesthesia to pin prick Microscopic study of smear revealed myriads of Hansen bacilli

portance and while they resemble tinea versicolor their true nature can be established by a microscopic examination They may resemble the annular lesions of ringworm but they spread more rapidly are pigmented and while hyperesthetic at first later lose their pigment and sensitivity They may resemble psoriasis since both lesions have red scaly raised margins but the anesthesia the depigmented

SIGNS AND SYMPTOMS

In a study of 743 patients with leprosy (34) Sloan reports the following more frequent presenting symptoms macules (344) nodules (97) anesthesia (64) ulcers (63) swelling of the skin including the hands (44) muscle weakness (31) contracture of fingers (28) erythema (17) swelling of foot or leg (14) atrophy of digits (9) and obstruction to breath-

center and the presence of the bacilli in the corium should make the diagnosis clear The anesthesia and the finding of bacilli in the corium also serve to differentiate the disease from lupus erythematosus

After a variable period the patches become nodular and about the size of a pea or form plaques many inches in diameter In white people these lesions are "ham colored" Their centers are anesthetic to heat and pain, devoid

The septum of the nose may be destroyed The exanthems of leprosy heal slowly in some cases the nodules ulcerate and discharge a yellow pus Sometimes areas of skin acquire a swollen erysipelous like appearance Areas of anesthesia may increase in size temperature sense being lost first, then by pain and tactile sense Pressure sense is rarely lost The lymphatic glands are swollen and have a characteristic elastic feeling



Fig 152 Reddish brown patches diagnosed erythema multiforme until examination demonstrated anesthesia to pin prick Microscopic study of smear revealed myriads of Hansen bacilli

of hair, and greasy looking *The commonest* sites are the face, back of the hands, and feet cheecks lobes of the ears and in some cases the nose forehead and chin The scalp is never involved Nodules may appear where none were before, and in rare instances the body becomes covered with small nodules As the lesions progress they obliterate the natural creases of the skin and cause ridges which give the face the characteristic leonine appearance

Nodules or lepromata spread to the cornea and anterior chamber from the conjunctiva destruction of the iris and ciliary body follows Nodular infiltration of the nasal mucosa occurs with rhinitis, epistaxis, and aphonia Sooner or later the lepromata invade the spleen, liver, testicles and nerves The fingers become shortened as a result of the absorption of the phalanges

The neural or anesthetic type of leprosy is a

milder disease than the form already discussed It may be accompanied by an exanthem, and macular lesions are commonly found early in the disease There may be a slight paralysis of a few facial muscles or part of a hand The earliest symptoms are burning tingling neuralgic pains formication hyperesthesia and later anesthesia and lymphadenitis There may be a palpable fusiform swelling on the ulnar and other large nerves disturbances of the skin ulceration, reduction of joint movement and shortening of the fingers and toes caused by bone absorption Contraction of the fingers may result in the "leper claw" or main en griffe Deformity of the nails results in a talon like appearance There may be perforating ulcers of the sole Various degrees of facial paralysis are seen, ranging from inability to close one eye to complete loss of function of the facial muscles

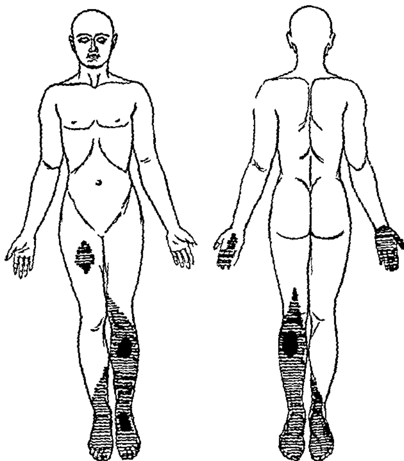


Fig 153 Patchy Asymmetrical Anesthetic Areas in the Polyneuritis of Leprosy

such as the anterior tibial peroneal, median radial, brachial great auricular and cervical nerves The nerves may be seen as well as felt just beneath the skin They are very tender to pressure but later become anesthetic The temperature of the involved fingers or toes is about 3° or 4°F lower than normal Atrophy of certain groups of muscles is followed by contracture of their opponents There follows distortion loss of power trophic The nerve lesions of leprosy are irremediable neural leprosy runs a chronic course and may be associated with long periods of inactivity

DIAGNOSIS

Leprosy may be identified by the lesions of the skin and mucous membranes and by its neurological manifestations Confirmation by microscopic examination is usually possible in cutaneous and mixed types of the disease

but may be difficult or impossible in maculo-anesthetic and neural cases There are no reliable serologic or skin tests It should be remembered that many lepers show both a positive serologic test for syphilis as well as a tuberculin reaction The diagnosis of leprosy can be confirmed by examination of scrapings from the nasal mucosa, histologic examination of excised pieces of infected cutaneous tissue, and microscopic examination of tissue fluid for the acid fast bacilli

McCoy has cautioned against placing too much dependence on the findings of nasal smears alone since many not suffering from leprosy have acid fast organisms in their nasal smears Sections of excised tissue from suspected areas may be taken, after careful preliminary cleansing of the skin in order to avoid contamination with saprophytic acid fast bacilli Smears from active lesions in the corium will usually reveal the acid fast bacilli An excellent method of obtaining material for microscopic examination is the incision and scraping of a nodule or of an area of thickening or discoloration The desired area is picked up and compressed between the fingers to render it bloodless A small incision, not more than one sixteenth of an inch in depth and one quarter inch in length, is made with a safety razor blade By a gentle scraping motion of the blade held at an angle *to the sides of the incised wound, material is* obtained and transferred to glass slides and stained in the same way as is the tubercle bacillus The acid fast organisms will be readily recognized

In early neural cases the diagnosis may be extremely difficult and years may elapse before it can be confirmed *Signs suggesting the disease* are localized hyperpigmentation patchy anesthesia depigmentation enlargement of the nerve trunks, and evidence of neural involvement Residence at some time in an endemic region should arouse suspicion especially if there has been leprosy among contacts or close associates of the suspected patient Some cases will require protracted observation and investigation before a correct diagnosis can be made, since diverse neural phenomena may be present for years before the pathognomonic cutaneous lesions appear Chronic granulomatous lesions not unlike tuberculosis are frequently found The histologic picture is that of tubercle formation Frazier has aptly said that the most typical cutaneous tubercles are found not in tuberculosis, but in leprosy In tuberculosis however, the acid fast bacilli will not be found in tissue specimens, and injection of this material into guinea pigs will result in tuberculosis

DIFFERENTIAL DIAGNOSIS

The differential diagnosis should exclude the following diseases syphilis, ringworm, lupus erythematosus, vitiligo, sarcoid, tuberculides, erythema nodosum erythema multiforme, pellagra acrodynia, syringomyelia, polyneuritis progressive muscular atrophy, filarial elephantiasis mycosis fungoides and espundia It may not be superfluous to point out that lepers may suffer also from syphilis and tuberculosis

TREATMENT

All authorities agree that a regulated way of living free of the constant dread of detection, good food, kindly care, rest and protection from injury outside an endemic area offer the patient the best chance for recovery and are surely potent auxiliaries in any management of this disease Many believe that specific medication is of minor importance

Complications should be treated and pyogenic infections and gangrenous parts may need surgical excision *Tracheotomy may* be necessary for laryngeal stenosis Infiltrated or ulcerated vocal cords often return to nearly normal condition under the influence of the rest obtained by this operation There is no objection to the removal of nodules purely for cosmetic purposes Indolent ulcerations of the extremities are benefitted by the application of a Unna boot using *Unna's paste* For the technique of administration see page 320

Chaulmoogra oil has been universally used in the treatment of leprosy but the results have been disappointing If for some reason its administration should be desirable, it can be given in gelatin capsules the initial dose being five drops three times daily and increased to tolerance Some patients can tolerate 100 drops three times daily Faget Johansen and co workers (28) recently report promising results with *promin* While they do not state that it has any specific action on the Hansen bacillus, they consider it an advance in the

right direction in the chemotherapy of leprosy and hope that further synthesis of the sulfa chemicals will produce a product which has specific properties against the M leprae Because leprosy is a chronic disease subject to periods of spontaneous remissions which may be prolonged it is very difficult to estimate the worth of any new treatment However these writers believe that the large numbers of patients showing improvement in contrast to the small number in whom unfavorable progress was made under promin therapy, cannot be explained on the basis of spontaneous improvement alone The drug can be safely administered intravenously for prolonged periods provided the blood and urine are examined frequently Hemolysis may result but it is usually controllable and is not a cause for discontinuance of treatment As yet no case of leprosy has become arrested under the influence of promin and the writers conclude that further experimental and clinical studies on the treatment of leprosy must be conducted before more definite conclusions can be drawn concerning its therapeutic value

Faget has reported the sulfonamides as being of value in the treatment of secondarily infected skin lesions of leprosy

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Chapter XV

TROPICAL DISEASES OF POSTWAR IMPORTANCE

General Considerations

In this country purely tropical diseases are seen only rarely Many diseases are prevalent in the tropics today which are not frequently seen in other parts of the world Some of the greatest scourges of the past have been eradicated from the temperate climates and pushed back into the tropics where under general unsanitary environmental conditions they still flourish Public health authorities for some time have been concerned and on the alert against the introduction or reintroduction of these diseases into areas now free from them Modern fast travel in its present tremendous volume presents great possibilities for this With thousands of our armed forces returning from tropical regions many cases of tropical disease are to be expected to appear among them Consequently, in a relatively short time many physicians in private practice and at hospitals in this country will see many such cases The civilian physicians of our country may also expect to see occasional cases among travelers returning from the tropics

In this chapter therefore those diseases which are most likely to be seen and to cause confusion will be discussed No attempt to be all inclusive will be made and some minor local tropical diseases will not be considered Sprue has already been discussed with the other nutritional diseases Typhus although prevalent in some tropical localities is world wide in its distribution and is discussed with the infectious diseases Weil s disease has been discussed in the disorders of the gastro intestinal tract

Neurasthenia and psychoneurosis are very important causes of disability They have been believed by some to cause nearly fifty per cent of the disabilities of Europeans in the tropics The manifestations do not tend to assume any special form and the preferable treatment is to return the patient to his natural environmental condition as soon as possible before the functional manifestations become fixed Otherwise their treatment is the same as has been discussed under Nervous and Mental diseases

The Diarrheal Diseases

CHOLERA

Cholera is an acute infectious enteric disease caused by the *Vibrio cholerae* or comma bacillus It is endemic in Asia and throughout the Far East and takes a fearful toll of life in the regions of the Ganges delta It still occurs in dangerous proportions in China, the Philippines Thailand, Indo China and Burma Since ancient times many pandemics have originated in endemic centers in India and have spread over both tropical and temperate regions of the world

Transmission

The disease is transmitted through the ingestion of food or drink contaminated with the infectious agent by contact with infected persons carriers or articles freshly soiled by their discharges or by flies Cholera has a roughly seasonal incidence being most prevalent during periods of high temperatures and greatest rainfall The *Vibrio cholerae* is present in great numbers in both the vomitus and stools of infected persons

Clinical Course

After an incubation period of from one to five days (usually three) during which there may be some malaise the onset is abrupt with violent diarrhea fever vomiting prostration and cramps in the lower extremities The stools lose their yellow color and become watery being ejected like water from a tap They are called rice water stools because they are transparent and opalescent and contain flecks of mucus There may be fifty stools a day and as a consequence the patient soon becomes dehydrated and weak Hemo concentration soon follows, the red blood cell

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Specific Diagnosis

The specific diagnosis is made by identification of the comma bacillus in the stools. In over half of the cases they may be detected in smears made from the "rice bodies" in the bowel discharge. Their comma-like morphology and characteristic "fish in a stream" arrangement is unmistakable. Some strains are easily detected in hanging drop preparations. Specific immune reactions must be employed for the specific diagnosis. Those employed are the *cholera red reaction* (of presumptive value because the reaction may be given by other vibrios), the *agglutination reaction* and the Pfeiffer *phenomenon*. The agglutination test is the most simple and practical but in doubtful cases the Pfeiffer phenomenon is of great value. For the performance of the agglutination test material obtained from the stool of the patient and a serum with a titre of at least 1:4000 should be used. It should agglutinate cholera organisms in a dilution of at least 1:500 or 1:1,000.

Management of the Cholera Patient

The general measures should include rest in bed with heat applied to the abdomen and extremities as long as required. The foot of the bed should be elevated. *Morphine* grain ¼ and *atropine* grain 1/150 are used for premonitory diarrhea. Vomiting may be relieved by the administration of *kaolin* 7 ounces in 14 ounces of water given in frequent sips or about one pint per hour. *Potassium permanganate* is recommended for the neutralization of the toxin of cholera. Two grain tablets, salol-coated, are given every half hour until the stools turn green. The blood pressure is maintained by the administration of parenteral fluids. When the patient can tolerate food the *diet* should be of low residue and supplemented with *ascorbic acid* (100 mg daily) and with a *vitamin B complex* concentrate.

It is desirable to estimate the *specific gravity of the blood* in order to control accurately the amount of saline given. This can be done by several methods. One popular method prepares a series of solutions of glycerin and distilled water with specific gravities ranging from 1.050 to 1.070 in gradations of 0.002. Small portions of these solutions are placed in flasks or test tubes and one drop of the patient's blood is added to each bottle. The specific gravity of the blood is indicated by the bottle in which the drop of blood neither rises nor sinks. The normal specific gravity of the blood is 1.056 to 1.058. A more accurate method developed by Phillips and his associates of the Navy Research Unit, Rockefeller Institute for Medical Research, uses copper sulphate and three or four drops of blood. The only apparatus required are a medicine dropper and several small bottles for the copper sulphate solutions. The technique consists in letting drops of plasma or whole blood fall into a graded series of solutions of copper sulphate of known specific gravity and noting whether the drops rise or fall in the solutions. Each drop upon entering the solution becomes encased in a sack of copper proteinate and remains a discrete drop without change of gravity for 15 or 20 seconds, during which its rise or fall reveals its gravity relative to that of the solution. The size of the drops need not be constant, hence no special pipette is needed. No temperature correction is required because the temperature coefficient of expansion of the copper sulphate solutions approximates that of blood and plasma. This method is capable of measuring gravities to ±0.00005, which is ten times the accuracy required. The solution automatically cleans itself after each test, because within a minute or two after the test is completed the material of the drop settles to the bottom as a precipitate.

The following hypertonic solution is suggested for intravenous administration:

Sodium chloride	13.75 gm.
Calcium chloride	0.25 gm.
Distilled water	1,000.00 c.c.

This replaces the salts lost by diarrhea and assists in retaining the fluid in the blood vessels, thus maintaining the blood pressure and also increasing the output of urine. It is given slowly and continuously, the amount being determined by the specific gravity of the blood as follows:

Specific gravity of the blood 1.062 Give 1,000 c.c.
Specific gravity of the blood 1.063 Give 1,500 c.c.
Specific gravity of the blood 1.064 Give 2,000 c.c.
Specific gravity of the blood 1.065 Give 2,500 c.c.

count may reach 6 000,000 from reduction in the amount of blood plasma the white blood cell count may be 50 000 the tissues become shriveled, the eyeballs sunken the sclerae injected and a moribund expression appears, which is called the "cholera facies" The skin becomes ashen gray and covered with a clammy perspiration, the pulse may be imperceptible The patient may die from collapse within twenty four hours The blood pressure is low and sometimes unobtainable average mortality in an epidemic is about 50 per cent With early treatment the mortality may not exceed 20 per cent

Diagnosis

In an epidemic there is little danger of mistaking the diagnosis *Acute arsenic poisoning* may closely simulate cholera, although in the latter the characteristic garlic odor is not detected on the breath In the tropics, *severe diarrheas* called *"cholera nostras"* are seen

TABLE L

	Cholera	Food Poisoning
Diarrhea	Painless pseudo-vomiting	Associated with some intestinal pain. Follows vomiting
Vomiting	Causes no distress watery and projectile Follows the diarrhea	Often violent and distressing Vomitus consists of food and is never watery copious nor projectile Generally precedes the diarrhea
Nausea	Absent	Constant
Retching	Rare	Constant often severe
Abdominal Pain	Rare	Constant
Tenesmus	Absent	Common
Stools	Watery and copious	Liquid fecal and offensive never colorless and copious
Urine	Complete suppression	Never suppressed
Muscular Cramps	Constant and severe	In very severe cases only and confined to the extremities
Collapse	Frequent chiefly from loss of fluids	Faintness and syncope from toxemia
Fever	Surface temperature below normal	Axillary temperature 99 to 102 F
Headache	Absent	Frequent

There is fever but usually it is not excessive There is a profound circulatory incompetence exhaustion and prostration the patient is unable to speak or make any voluntary movements There may be urinary suppression and usually a marked acidosis as a result of the loss of alkali in the stools If the resulting azotemia and dehydration are not corrected as well as the circulatory failure and anuria death will follow from respiratory failure vasomotor collapse or uremia The which resemble cholera in the early stages In these and isolated cases of supposed cholera positive identification of the *comma bacillus* is imperative *Algid* or *choleraic subtertian malaria* may simulate true cholera as may also acute bacillary dysentery when very severe and *sudden in onset* As the diagnosis of cholera from *mushroom poisoning* is important, table L from Manson Bahr may be of use (1)

ble cholera vaccine Revaccination with a "booster" dose should be done every six months while in the endemic area or prior to the cholera season The vaccine is given in two subcutaneous injections of 0 5 c c and 1 0 c c of vaccine from seven to ten days apart The booster dose is 1 0 c c

A new type of vaccine has been described by Jenning It consists of an entire liquid culture of the vibrio killed with phenyl mercuric nitrate and used directly in the original medium It has the advantage of simplicity in quantity production The cholera vaccines in present use are antibacterial but apparently stimulate no resistance to endotoxic substances

4 *Chemoprophylaxis* There is no evidence available that the sulfonamides or other chemotherapeutic agents are effective in the prevention of cholera

Amebic Dysentery—Amebiasis

Amebiasis is a disease of protean nature and symptomatology The etiologic agent is the *Endameba histolytica* Though it invades mainly the intestinal tract it may attack other organs and produce secondary metastases of which the principal is hepatic amebiasis Amebic dysentery is world wide in distribution but infections are much more common in the tropics and subtropics than in temperate regions The incidence may be high however in the latter regions when the sanitary conditions are poor The prevailing dysentery in the tropical and subtropical areas of America Asia, Africa, the West Indies, the Malay Archipelago and the Philippine Islands is due to amebic infection

MODE OF TRANSMISSION

The disease is transmitted by drinking contaminated water and by eating infected foods especially those that are commonly served cold or moist and hand to mouth transfer of the infected material from moist objects soiled with discharges of an infected individual or carrier There is a wide spread use in the Orient of human excreta for the fertilization of truck gardens It follows that one should avoid uncooked food or unboiled water if living in such areas where this practice is prevalent The disease is also transmitted by the droppings of flies and roaches as well as rats and other small animals The greatest incidence of the disease in the tropics is during the rainy season when there is more likelihood of contaminated water supplies

The *incubation period* is from 2 days in severe infections to several months in the subacute and chronic forms it is commonly 3 to 4 weeks The *period of communicability* exists during the course of the infection and until repeated microscopic examination of the stools shows the absence of *Endameba histolytica* (either trophozoites or cysts)

Craig estimates that about thirteen million people in the United States harbor *Endameba histolytica* While dysentery presents a dramatic and concrete clinical picture non dysenteric amebiasis constitutes the major problem The *symptoms* of amebiasis are bizarre and simulate those of other diarrheas The majority of cases are carriers with cysts the acute cases with a bloody diarrhea are rarer As a rule, there is little interference with the general health and periods of exacerbation alternate with periods of quiescence At least 50 per cent of those harboring Endameba histolytica are asymptomatic at the time of examination Carriers may complain of the following symptoms loss of weight constipation mild diarrhea colicky pain in the right lower quadrant dull headache and postprandial distress with muscle pains and backache The pain is usually localized to the cecum and sigmoid areas but also occasionally to the transverse colon The skin may be dull and there may be a subclinical icterus Hepatomegaly is not uncommon

In the acute attack there is a sudden onset of diarrhea or there may be several days of soft mushy stools before watery diarrhea develops There may be chills vomiting tenesmus and an intense desire to defecate but only mucus and blood are passed The stools may reach twenty in a twenty four hour period but they are usually less than twelve The continuous diarrhea with its loss of body fluids is soon reflected in the patient who becomes exhausted and prostrated Rarely, a fulminating course causes death in a few days

In atypical cases there may be constipation lassitude and anorexia with easy fatigability yet no obvious signs of disease or abdominal involvement The disease is often latent the infection apparently subsiding with apparent

The injections are given every four hours until the specific gravity of the blood falls below 1 062 Recently blood plasma or reconstituted plasma is being used by the continuous drip method If the patient is dehydrated, and one is unable to estimate the specific gravity of the blood hypertonic saline can be given intravenously, using judgement as to the amount to be given An alternative method, provides for normal saline to be given intravenously every four hours, if hypertonic saline cannot be prepared

The fever toxemia starvation and loss of body substance will result in a markedly negative nitrogen balance After rehydration and replacement of electrolytes it may be desirable to give transfusions of isotonic plasma or albumin in order to maintain an adequate plasma protein concentration Whole blood transfusions are also beneficial to sustain both plasma protein and hemoglobin concentrations Frequently diarrhea and vomiting are aggravated by the oral ingestion of food in which case amino acids (Amigen) may be added to the intravenous infusion up to a 3 per cent concentration If Amigen is given too rapidly by infusion nausea vomiting and hyperthermia may result

The effectiveness of early supportive therapy may be obtained from the following laboratory determinations hematocrit hemoglobin plasma specific gravity or plasma protein determinations (copper sulphate method) blood or serum NPN, and serum CO_2 content and chloride concentrations

There is no unanimity of opinion as to the efficacy of the sulfonamides Beneficial results with sulfaguanidine have not been striking but a clinical trial with sulfadiazine may be justified The use of sulfadiazine however carries with it the hazard of urinary complications if it is administered prior to the resumption and maintenance of an adequate flow of urine

Shock Shock and collapse are controlled by the addition of 50 gm of glucose (dextrose) to each 1000 c c of saline solution administered To this should be added thiamine chloride 3 mg ascorbic acid 50 mg and nicotinic acid amide 15 mg These can be given in the glucose solution or by mouth If *normal human serum* or *plasma* is available it should be administered intravenously for the control of shock but not as a substitute for other fluids which are essential

Acidosis and Suppression of Urine To combat anuria or marked acidosis the following solution is recommended for intravenous administration

Sodium chloride	5 ,6 gm
Sodium bicarbonate	18 25 gm
Distilled water	1 000 00 c.c

This solution should not be boiled or autoclaved since the high temperatures will change the bicarbonate to caustic soda The following technique may be used for sterilization

1 The sodium chloride should be dissolved in the distilled water and sterilized by boiling
2 Remove from the heater and at once add the sodium bicarbonate which has been taken from the original container and weighted in a sterile container The solution should be cooled to body temperature and used at once The solution should be prepared and administered with great care and the patient observed with care for signs of tetany or other manifestations of alkalosis

Prevention

1 General measures in areas where cholera is endemic include (a) maintaining a satisfactory water supply by chlorination or boiling (b) avoidance of uncooked foods (c) meticulous control of the milk supply (d) adequate fly control measures and (e) detection and isolation of carriers

2 The isolation of patients and carriers should conform to rigid enteric disease isolation standards Bacteriological examinations should be carried out on the stools of all contacts to determine carriers Attendants should observe rigid personal prophylaxis by scrupulous cleanliness disinfection of the hands each time after handling the patient or touching articles contaminated by dejecta and the avoidance of eating or drinking any thing in the room of the patient Those attending the patient should be prohibited from entering the kitchen or space where food is prepared

3 *Immunization* Those entering endemic areas should be immunized with a suita

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recovery in the absence of treatment for several years Chronic amebiasis may persist for years with little else than chronic debilitation, it may also be accompanied by frequent acute exacerbations, or, the organisms may invade the liver and give rise to liver abscess Amebic ulcerations of the rectum may simulate carcinoma

The lesions of amebiasis occur predominantly in two regions namely, in the cecal appendix and the rectal sigmoid D Antoni (2) believes on this basis that amebiasis should logically be classified as follows

1 Asymptomatic Amebiasis
   The patient has no symptoms and the lesions are not confined to specific areas
2 Symptomatic Amebiasis
   A Asyndromic—Mild toxemia and vague gastro intestinal irritation, with lesions not confined to specific areas
   B Syndromic—Symptoms simulating chronic appendicitis, peptic ulcer, chronic cholecystitis with lesions usually confined to the cecal area
   C Dysentery—(Acute or chronic) Symptoms of dysentery, with lesions throughout the colon, especially the rectum and the sigmoid
   D Hepatitis and Liver Abscess—Fever, pain and tenderness in the liver area, with lesions in the liver tissue
   E Involvement of other organs—abscess of lung brain, kidney and amebiasis cutis

Several factors are worth noting in the cases of liver abscess The large number of stools found negative for *E histolytica* indicate that a negative fecal examination does not exclude the diagnosis of amebic liver abscess Diarrhea occurs in only a small percentage of patients The presence of fever of undetermined origin and hepatic symptoms including pain tenderness with or without hepatomegaly, should suggest amebic hepatitis with or without abscess formation When *liver abscess* occurs there is usually fever leucocytosis hepatomegaly, right upper quadrant tenderness with a dull aching pain referred to the right shoulder and an increase in the area of liver dullness Liver abscesses may be single or multiple they are most commonly found in the right lobe The amebae invade the liver by way of the portal vein They may often be seen in the portal capillaries, more rarely invasion may take place directly from a penetrating ulcer which is in actual contact with the surface of the liver

The Endamebae invade principally the mucous membrane of the colon where they enter the crypts of Lieberkühn, secrete a cytolysin and penetrate to the submucosa The typical amebic ulcer has a ragged undermined edge, it varies greatly in size and may extend down the rectum to the anal margin Small submucus abscesses form ulcers in the long axis of the cecum hepatic flexure, rectum or splenic flexure The lower portion of the small bowel is rarely involved The ulcers may perforate and cause peritonitis or a localized pericolonic abscess Craig and Faust mention three pathognomonic features of intestinal amebiasis (1) nodular thickenings situated at the summits of the folds of mucous membrane containing gelatinous material in which motile trophozoites are found (2) ulcers with ragged undermined edges, the ulcer floor which is formed by the submucosa or muscularis layers of the intestine and covered with necrotic tissue containing the amebae, and (3) the presence of sinuses beneath the mucous membrane connecting the ulcerations

DIAGNOSIS—AIDS IN THE CASE STUDY

The clinical diagnosis may be unreliable the most important single procedure in the diagnosis of amebic dysentery is the demonstration of the amebae in the stool The following procedures may be helpful

Culture Techniques Boeck and Drobohlav have devised a culture technique but its use in diagnosis has given inconsistent results (3)

Complement Fixation Reaction Craig has demonstrated that the blood sera of persons harboring *E hystolytica* contain specific complement fixing properties The difficulty of obtaining a potent antigen and the necessity of using the human hemolytic amboceptor render this test impracticable for clinical application at present Craig has emphasized that the test should not replace the diagnostic demonstration of the causative organism

Saline Purgation Andrews (4) has shown that by the examination of a single specimen of the stool following saline purgation, the organism can be detected in 75 per cent of

those cases found positive by the examination of six consecutive stools passed without a cathartic

Sigmoidoscopic Examination While some investigators have found sigmoidoscopy of value, others believe that a specimen of the stool following a purgative and anema is superior to the sigmoidoscopic examination

Stool Examination The diagnosis from specimens of the stools has long been hampered by the lack of a suitable concentration technique Zinc sulfate centrifugal flotation provides a simple and efficient means for laboratory diagnosis Since all concentration techniques fail to detect trophozoites the zinc sulfate concentration should be combined with one of the direct fecal film techniques

A fleck of stool from the specimen is mixed with a drop of saline and streaked across a glass slide, over one half of which a cover slip is then placed A small drop of iodine eosin stain is mixed with the streaked material on the remaining portion of the slide and covered with another cover slip The specimen is then examined under the microscope If one finds actively motile amebae containing red blood cells with hyaline pseudopodia it is most likely *E hystolytica* There are two non pathogenic amebae found in the gastro-intestinal tract which may be confused with it namely *E coli* and *E nana*

ROUTINE DIAGNOSTIC PROCEDURES

1 Three stools passed naturally should be examined and if negative, the patient is given a saline purgative before he retires and a sample of feces is collected the following morning at 6 A M

2 Sigmoidoscopy One and one half hours before sigmoidoscopy and enema of 1 liter of normal saline is administered, following evacuation the enema is repeated and a specimen from the last portion of the second enema is collected Sigmoidoscopy is then performed the mucosa inspected and material aspirated from suspicious areas by means of a glass tube attached to a rubber suction bulb

3 The two fecal specimens should be examined by means of the direct fecal film and the zinc sulfate centrifugal flotation techniques and the aspirated sigmoidoscopic material by the direct fecal film The aspirated material and second enema specimen are to be utilized for Shigella culture

TREATMENT

Unfortunately the necessity of treating asymptomatic patients is not generally realized in spite of the fact that these patients may develop acute symptoms at any time They excrete the infective cystic stage and spread the infection D Antoni points out that following the medication pre treatment symptoms may persist for as long as four months This does not warrant more treatment, however unless the causative organism can be *recovered from the patient After treatment*, from twelve to fifteen stools should be examined over a period of six months D'Antoni suggests the following drugs to be used (2)

- Asymptomatic Amebiasis *Chiniofon* or *Diodoquin* —if either of these drugs fail *Carbarsone* or *Vioform* is indicated
- Symptomatic Amebiasis *Chiniofon* or *Diodoquin* If either of these drugs fail try *Carbarsone* or *Vioform* If severe abdominal distress is encountered *Neoprontosil* is recommended
- Dysentery (Acute or Chronic) *Neoprontosil* in conjunction with *Chiniofon* or *Diodoquin If either of these drugs fail Carbarsone* or *Vioform* is indicated
- Hepatitis and Liver Abscess *Emetine* and treatment as for symptomatic amebiasis Surgical procedures may be indicated in amebic liver abscess
- Involvement of Other Organs *Emetine* followed by *Diodoquin* or *Chiniofon*

Dosage of Drugs Used

Carbarsone Four grains (1 capsule) twice daily for ten days children are given 1 grain daily per 20 pounds of body weight The drug is given following the morning and evening meal for 10 days If *E hystolytica* is still present the course may be repeated after a 10-day rest period The drug is 90 per cent effective If intestinal bleeding occurs it should be stopped *Contraindications* for the drug are the presence of liver or kidney disease

Chiniofon (Anayodin and Yatren) The dosage is 16 grains (4 tablets) following meal by mouth for seven days The children s dose is 1 grain three times daily per 10 pounds of

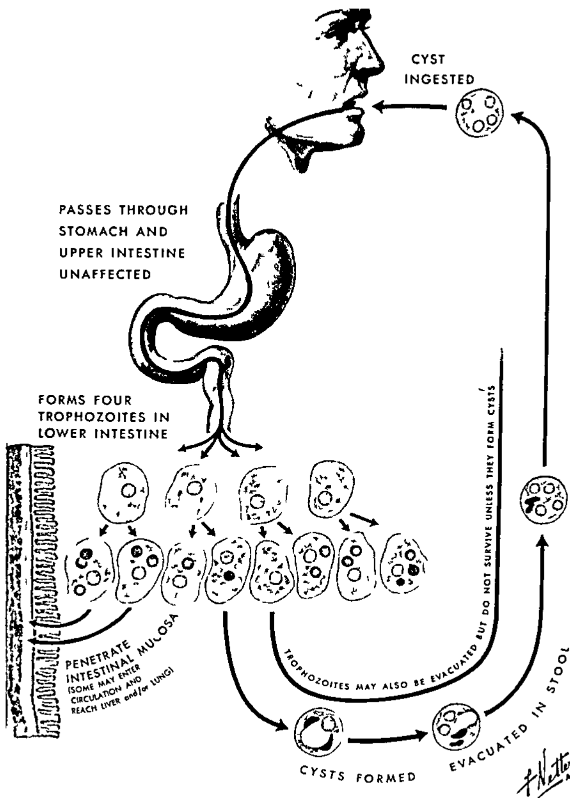


FIG 154 Life cycle of the endamoeba histolytica The cysts are swallowed and pass intact through the stomach and upper part of the intestine In the lower part of the small intestine each cyst forms four trophozoites and these divide and multiply by fission They are motile and ingest red blood cells Some of them penetrate the mucosa of the intestine by means of a lytic ferment which they secrete ulcers are thus formed They may be carried by the blood stream to the liver where they form abscesses Other trophozoites form cysts which pass out in the stool These cysts in their first phase are uninuclear but later they form two and then four nuclei Their large food vacuole is absorbed If the bowels are very active some of the trophozoites also are excreted These may perish or form cysts outside the body and survive

(Courtesy The Seminar published by Sharp & Dohme Inc)

body weight. If no amebae are found in the stools over a period of up to six months, medication can be stopped. However, if the stools remain positive the treatment is repeated after a rest period of one week. The drug is considered 90 per cent effective. Diarrhea may appear on the second or third day following administration of the drug but it lasts only a few days and may be controlled by 2 drams *tincture of camphor* or 2 to 6 drams of Kaomagma following each defecation. There are no contraindications.

Diodoquin. Adults are given 22.5 to 30 grains (7 to 10 tablets) daily for two or three weeks after meals. Children are given the equivalent of one tablet daily per 15 pounds of body weight. The tablets may be chewed. If after three weeks the organisms are still present, the course is repeated after a rest period of one week. Only severe cases will require hospitalization. The drug is said to be from 80 to 90 per cent effective. There are no untoward symptoms reported nor are there any contraindications to the drug.

Emetine Hydrochloride. 1 c.c. of the solution contains 1 grain of emetine hydrochloride. The adult dose is 1 grain subcutaneously for twelve successive days. It may be supplemented by 0.5 grain orally. In children over 8 years of age the dose should not exceed ½ grain daily. It is not given to children under 8 years of age. A rest period of one month should intervene before the course is repeated. Contrary to a statement frequently seen in the literature, there is no convincing evidence that *E. histolytica* becomes emetine-fast.

The symptoms are relieved in about 80 per cent of cases; the drug is curative in only some 30 per cent of cases. It is fairly efficient in the treatment of liver abscess. *Toxic symptoms* are ankle or toe drop, sudden cardiac failure, muscular pains and weakness. When these appear the drug must be discontinued. *Contraindications* are myocardial, kidney and liver damage.

Neoprontosil. This drug is combined in selected cases with Diodoquin or Chiniofon. The adult dose is from one to three 5 grain tablets three times daily for 5 to 7 days. Children are given 1 grain three times daily per 10 pounds of body weight. The drug should be stopped when abdominal distress is relieved.

D'Antoni reports this drug is 50 per cent effective in 50 unselected cases.

Vioform. The adult dose is one 4 grain capsule three times daily for ten days. In severe infections this dose can be doubled. The dose for children is ½ grain three times daily per 15 pounds of body weight. After a rest period of one week the course can be repeated. It is reported to be 80 per cent effective. It is more toxic than Chiniofon, less toxic than Carbarsone. Diarrhea may appear after a few days of administration; it is managed as set forth under the discussion of Chiniofon.

The following treatment, employing slightly different dosages of the drugs mentioned, is that suggested by a Circular Letter No. 56 issued by the Surgeon General of the War Department, Washington, D. C.

For Ameba Carriers without Dysentery

Either carbarsone or chiniofon may be prescribed. *Carbarsone* 0.25 gm. by mouth twice daily is administered for 10 days. A soft diet is recommended where possible. The activity of the patient should be restricted. Toxic symptoms are rare and may consist of abdominal distress, nausea, vomiting, and exfoliative dermatitis. *Chiniofon* is prescribed 1 gram orally three times daily for 10 days. Soft diet and rest in bed is advised. Chiniofon is more effective and less toxic than carbarsone.

Seven days after completion of treatment, the stools are examined on three consecutive days for cysts. Similar examinations are made once weekly thereafter and subsequently on three consecutive days after a rest period of three months. If not cured, the treatment is repeated.

For Acute or Chronic Amebic Dysentery

Emetine hydrochloride 0.06 gm. is prescribed for intramuscular (subcutaneous is preferred by many) administration twice daily or 0.06 gm. once daily for 4 to 6 days. Vomiting may occur as a toxic symptom; it is controlled by sedatives. Other effects are acute myocardial degeneration, peripheral neuritis usually from prolonged treatment, and in some cases a rapid drop in blood pressure will be noted accompanied by fainting spells. Emetine is employed only to control the acute symptoms of amebic dysentery and therefore should be stopped as soon as the dysentery subsides.

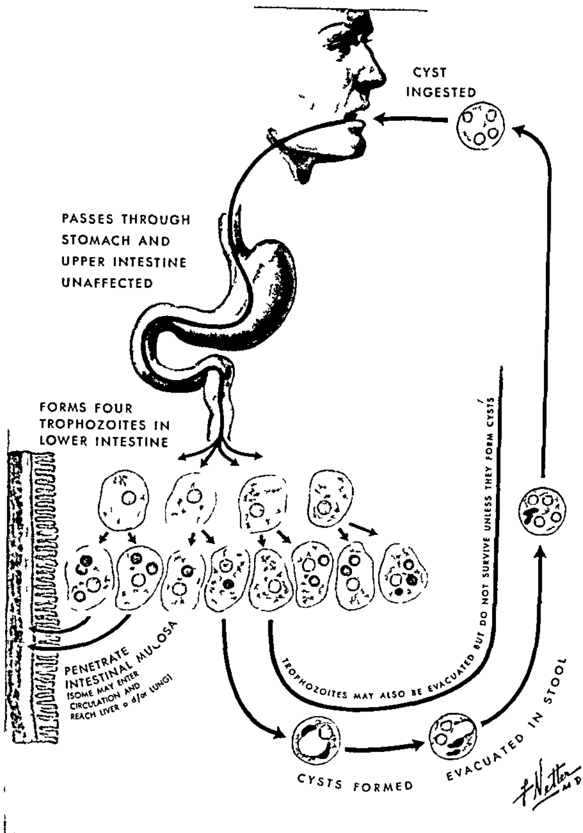


Fig 154 Life cycle of the endamoeba histolytica The cysts are swallowed and pass intact through the stomach and upper part of the intestine In the lower part of the small intestine each cyst forms four trophozoites and these divide and multiply by fission They are motile and ingest red blood cells Some of them penetrate the mucosa of the intestine by means of a lytic ferment which they secrete ulcers are thus formed They may be carried by the blood stream to the liver where they form abscesses Other trophozoites form cysts which pass out in the stool These cysts in their first phase are uninuclear but later they form two and then four nuclei Their large food vacuole is absorbed If the bowels are very active some of the trophozoites also are excreted These may perish or form cysts outside the body and survive

(Courtesy The Seminar published by Sharp & Dohme Inc)

tuted through the aspiration wound Open drainage should be avoided whenever possible Use *chiniofon* for the intestinal infection which probably exists Manson Bahr suggests the following *indications for open operation*

1 When after repeated aspirations no pus is obtained but the signs of its presence are too strong to be ignored
2 When the abscess points in the epigastrium indicating an abscess of the left lobe of the liver
3 When a large amount of pus is present is secondarily infected and has not yielded to aspiration

Pulmonary Amebiasis

This is discussed in Chapter IX See page 517

Amebic Abscess of the Brain

Amebic abscess of the brain is rare but generally fatal it is usually secondary to liver abscess It may respond to emetine therapy

Bacillary Dysentery

Bacillary dysentery is an acute infectious disease which in its most severe form is caused by the dysentery bacilli *Shigella dysenteriae* *Shigella para-dysenteriae* and other species of the genus *Shigella* Bacillary dysentery exists throughout the civilized world especially in unsanitary localities Its *incidence* is highest in tropical and subtropical regions The *source of infection* is the bowel discharge of an infected person or carrier Healthy carriers are common The disease is *transmitted* by eating contaminated food and by hand-to-mouth transfer of contaminated material by flies from objects soiled with discharges of an infected person or of a carrier by drinking contaminated water The *incubation period* is from 3 to 7 days The *period of communicability* is that period during the acute phase of the disease until the micro-organisms have disappeared from the bowel discharges While as a rule the stools rapidly become negative patients may become chronic carriers Susceptibility is general among children it is less so in adults A relative and not permanent immunity follows recovery from the disease

The disease starts as an acute diarrhea in severe cases with fever tenesmus cramps and frequently watery stools containing pus mucus and blood The patient may become delirious or go into rapid collapse The disease is more or less self limiting running its course in from ten days to two weeks Ulceration of the colon may progress to stenosis The colon is chiefly involved although the terminal portion of the ileum also frequently reveals inflammatory changes with hemorrhage and sloughing of the crest of the mucosal folds which result in the formation of large irregular penetrating ulcers Perforation is very rare in contrast with the ulcers of typhoid fever

SPECIFIC DIAGNOSIS

The diagnosis depends upon the identification of the etiologic agent in stool cultures The selective desoxycholate agar (citrate) and the S S agar make diagnosis more accurate than was formerly possible Both these agar media are available in dehydrated form and are easy to use At least one of these should be used in the bacteriological examination of the feces of a suspected case When the organism is isolated biochemical and immunological tests should be utilized for identification

Freshly passed stools are best for the isolation of the *Shigella* Rectal swabs can be used for plating at the bedside When this is not possible the material can be collected in 30 per cent glycerol in saline which will act as a preservative for from 24 to 36 hours Agglutination tests cannot be used as an absolute test of infection or immunity for any member of the *Shigella* group

TREATMENT

The *antisera* available are not type specific and are of little if any value in the treatment of bacillary dysentery Various sulfonamide compounds have been used with varying degrees of succes *Sulfasuxidine* (succinylsulfathiazole) one of the newest sulfonamides has shown promise of being an effective agent against the infection The basic daily adult dose has been shown to be 3 grams three times daily When there is much watery diarrhea, it is well to double the initial dose The treatment can be stopped when two consecutive negative stool cultures have been obtained using the highly selective culture media mentioned before When cultures are not possible

Simultaneously with the administration of *emetine*, give *chiniofon* or *carbarsone* by mouth in the dosage mentioned before If the treatment is ineffective because of the lesions of the lower colon or rectum, these two last named drugs should be given as a retention enema as follows

- *Carbarsone* by rectum 2 0 gm dissolved in 200 c c of a 2 per cent sodium bicarbonate solution Retention may be aided by a mild sedative This should be given on five consecutive nights, if it proves irritating change to alternate nights
- *Chiniofon* can also be given by rectum, 3 0 *gm in 300 c c of sterile water, after a* cleansing enema of water
- *Caution* High enemas are not to be given as great damage may result due to the friability and ulcerative condition of the bowel Cases have been reported where the mere pressure of water (200 c c) has caused perforation

General Care For acute cases the patient should be kept in bed on a liquid diet, broth at first, and later adding milk, eggs and custard This is continued until the acute symptoms subside when he is given a soft low residue diet *For chronic cases, the patient is* kept in bed and given a soft low residue diet The full general diet can be resumed during convalescence

Amebic Hepatitis without Liver Abscess

Emetine hydrochloride is given as outlined before but is continued for 8 days If evidence of hepatitis persists after 8 days liver abscess should be suspected and aspirated if found If practicable, check the effect of emetine on the heart muscle by an electrocardiogram before the treatment and daily *from the fifth day on (look for changes in the* QRS complex and inversion of the T wave) Use *chiniofon* as mentioned before by mouth for intestinal infection which probably exists *Carbarsone* may be toxic in some cases of hepatitis

Amebic Liver Abscess

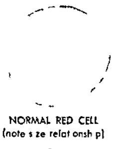
The diagnosis of amebic abscess of the liver is not always easy There may be no symptoms or there may be fullness, a feeling of weight and pain in the right hypochondrium night sweats loss of weight marked rheumatic pains at night and pyrexia As a result of *irritation of the endings of the phrenic nerve,* pain may be referred to the right shoulder or if the abscess is in the left lobe of the liver to the left shoulder There may be an increase in liver dullness usually in a downward direction Not infrequently, there is pleural effusion and a pleuritic rub There may be cervical, axillary and supraclavicular adenopathy A localized pain in the intercostal spaces especially, to applied pressure, is a sign of some diagnostic value These abscesses may rupture into a bronchus when there will be hemoptysis, prune juice sputum and coughing Rupture may also occur into the pleura pericardium, peritoneum, stomach, or colon, or through the skin

DIAGNOSIS

Liver abscess should be suspected when there is progressive ill health associated with pyrexia abdominal signs, night sweats and leucocytosis Roentgen study may reveal limitation or fixation of the diaphragm with some doming, tenting and alteration of the cardio-phrenic angle to a right angle A basal pneumonia in the right lung, especially, when *of low grade should suggest some intrahepatic* suppuration When these signs are present, a thorough examination of the feces should be made for the recovery of the organisms The liver may be aspirated for diagnostic purposes the needle being inserted at the point where the abscess lies closest to the skin, preferably between the 8th and 9th intercostal spaces in the right axillary line The needle is inserted upwards inwards, and backwards for about $3\frac{3}{4}$ inches *This will avoid puncturing the* inferior vena cava which is at least 4 inches from any part of the chest wall The needle will make an up and down pendular movement synchronous with respirations when the liver is entered At this point it should be gently advanced until a sense of resistance is felt which indicates that it has penetrated the abscess cavity A syringe is then attached to the needle and the pus aspirated

TREATMENT

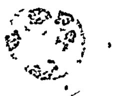
Emetine hydrochloride is given for 8 days The abscess is drained after about 4 days from the beginning of treatment The *aspiration* may be repeated or continuous drainage insti


NORMAL RED CELL
(note s ze relat onsh p)


TROPHOZOITE
(r g form)


TROPHOZOITE
(older form—Schuffner s dots prese t)

YOUNG SCHIZONT
(nuclei d d ng)


SCHIZONT (more ad anced)
(b own h p gment present)


MEROCYTES
(segments poorly defined)


MACROGAMETOCYTE (female)
(chromat n compact)


MICROGAMETOCYTE (male)
(chromat n d ffuse)

I lasmodium u av

PLATE IX
Malaria Para ites

chronic cases, and those considered as carriers are treated for five days Acute cases are given the drug, 5 grams four times daily for two days, then three times daily until the stools are normal for two days If a relapse occurs, the treatment should be repeated with *sulfadiazine*, *sulfathiazole* or *sulfaguanidine* in this order of preference The dosage advised in Circular Letter No 33 War Department, U S A February 1943 for sulfaguanidine is an initial dose of 3 5 gm followed by 3 5 gm every four hours day and night until the number of stools per day has been reduced to five or less Then, a maintenance dose of 3 5 gm every eight hours a day and night to be continued until the stools have been normal in appearance for ninety six hours If there is no improvement observed within seven days, the drug is discontinued Chronic cases are given 3 5 gm every eight hours day and night for not more than two weeks

In the very mild cases, little treatment is needed outside of rest in bed restriction of food for twenty four to forty eight hours sufficient liquids by mouth with sedation and heat to the abdomen to relieve any discomfort In the more severe cases, there is little reason to insist on calomel or castor oil when there has been a marked watery diarrhea *Sodium sulfate*, or *magnesium sulfate* has been used for over a hundred years and has won the approval of many competent physicians all over the world Sodium sulfate is given one or two teaspoonfuls of a saturated solution at four hour intervals for several days, for the purpose of eliminating the toxin of dysentery It will be found that after a few days that there is less straining and tenesmus the stool becomes more copious and the general condition of the patient improves This treatment can be continued until the stools become watery and then continued for a few days, one teaspoonful daily Some, including the author believe that in the presence of a very profuse diarrhea such treatment may be harmful and prolong the diarrhea

Diet For a few days the diet should consist *only* of liquids such as barley water, albumen water clear soups and boullion Milk and fruit juices should be avoided Gradually gruels rice broths tea and toast are added and later soft solids of low residue Alcohol or medicaments containing alcohol are forbidden The patient should not take any cathartic or laxative Other items which should be banned from the diet are cured or fried meats corned beef, dried beef, kidney, ham, pork, shellfish or veal highly spiced or seasoned foods, rich pastries, vegetables which have not been pureed cabbage, brussel sprouts, cauliflower corn, cucumbers lettuce, onions peppers, radishes sauerkraut, tomatoes, turnips or watercress

Cramps are controlled by paregoric In patients who are marasmic, the treatment should be directed to the general nutritional state and in these it is well not to restrict fluids In a mild or moderately severe case, the fluid intake should be about 3000 c c or more each twenty four hours and the diet free from residue In the acute fulminating cases, besides rest in bed and *sulfasuxidine* or one of the other sulfonamides mentioned it is well to administer intravenous glucose, 5 per cent in saline to which has been added thiamine chloride, 3 mg, ascorbic acid, 50 mg and nicotinic acid amide 15 mg These can be given orally or parenterally Enough fluid should be given to maintain a daily urine output of 1000 c c or more Severe abdominal pains are best controlled by *morphine* *Sodium bicarbonate* may be necessary to correct acidosis especially in young children 0 5 to 1 0 per cent solution in normal saline can be given intravenously

Severe tenesmus may be relieved by a suppository, the formula of which is

℞ Epinephrin 1 100	3 0 c c
Anesthesin	3 0 c c
Cocoa butter q s ad	20 0 c c

M Fiat suppositories No X
Sig Insert one every four hours as needed

Vaccines To date no satisfactory vaccine has been developed against bacillary dysentery There is evidence accumulating from work in the Orient and Europe that the oral administration of bacteriophage is of value and there is no contraindication to its use as a prophylactic measure in the face of an outbreak of epidemic proportions

Yellow Fever

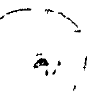
Yellow fever is an acute infection caused by a specific filtrable virus The source of infection is the blood of infected persons, monkeys and probably some other wild animals It is transmitted by the bite of infected *Aedes aegyp*



TROPHOZOITE
(single ring form)



TROPHOZOITES
(multiple infection)



TROPHOZOITE
(older form)



SCHIZONT
(young binuclear form)
rarely found in circulating blood



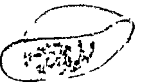
SCHIZONT
(older form)
rarely found in circulating blood



MEROCYTES
rarely found in circulating blood



MACROGAMETOCYTE (female)
(characteristic crescent shape)
(chromatin compact)

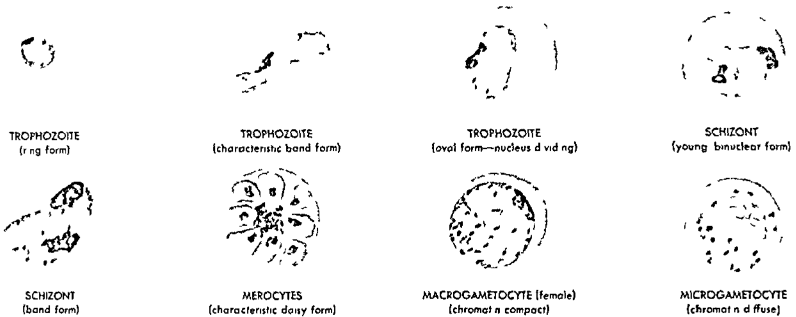


MICROGAMETOCYTE (male)
(crescent shape—chromatin diffuse)

Plasmodium falciparum

PLATE IX (*Continued*)
Malaria Parasites

(*Courtesy The Seminar published by Sharp & Dohme Inc.*)



Plasmodium malariae

PLATE IX (*Continued*)
Malaria Parasites

mosquitoes and a few allied species. The *incubation period* is from three to six days, rarely longer. The period of *communicability* is two days before and two or three days after the onset of fever. There is a high degree of communicability when infected mosquitoes abound and there are many susceptible persons. Recovery from an attack is regularly followed by immunity apparently for life. Brief *artificial immunity* may be attained by the use of convalescent serum. *Active immunity* is quickly developed by the use of modified living virus; its duration is uncertain but is believed to be several years.

GEOGRAPHIC DISTRIBUTION

Yellow fever has occurred previously in severe epidemic form in most of the countries of the Western hemisphere and in Africa. Serious outbreaks in Africa have been limited to the west coast, and this has been attributed to the absence of modern transportation. Within recent years it has been shown to be endemic in extensive jungle areas in tropical South America (Bolivia, Brazil, Colombia, Ecuador, Paraguay, Peru, Venezuela, possibly in the Guianas and elsewhere). Despite the fact that susceptible peoples and mosquitoes abound in the Orient, no explanation has been forthcoming for the failure of the virus to invade western countries. A case has not been reported in North America or Puerto Rico for many years. The transfer of the virus from jungle areas to rural or urban areas where *Aedes aegypti* breed and the inhabitants are susceptible, results in epidemics.

TRANSMISSION

Within recent years it has been shown that there are important differences between the mechanisms of transmission of endemic and epidemic yellow fever. The endemic disease, which for convenience has been called jungle yellow fever, probably is maintained in lower animals or arthropod reservoirs and probably is transmitted normally by insect vectors other than *Aedes aegypti*. In Brazil, for example, *Aedes scapularis*, *A. fluviatilis*, *A. leucocelaenus* and *Haemogogus capricornus* have been incriminated as effective vectors and the last two have been found naturally infected. Other species have also been proven to be efficient vectors in the laboratory. The epidemic disease, also known as urban or rural yellow fever, occurs when the virus has been introduced into communities of susceptible individuals where the vector, *Aedes aegypti*, is present in sufficient numbers. Any area where this mosquito exists is potentially liable to have epidemics of this disease. The breeding range of *Aedes aegypti* is between 40° N and 40° S latitude throughout the Old and New Worlds. This mosquito is domestic in its habits. It breeds by preference in artificial containers, especially those found around human habitations such as tin cans, flower vases, rubbish, cemetery urns, holy water fonts in churches and discarded tires. The mosquito is a day flying insect when young, but after drawing blood, becomes nocturnal.

CLINICAL FEATURES

The clinical features of yellow fever show great variety. In a population immune or partially immune the symptoms may be slight, not unlike influenza. The usual clinical picture is a sudden onset with fever reaching 104°F. on the 2nd day and dropping to between 98° and 99° F. on the 3rd to the 5th days. There is slow pulse in proportion to the body temperature which in rare cases may not reach its maximal proportion until the 8th day. Associated symptoms are photophobia, supraorbital headache, backache, ostalgia, epigastric pain, swollen flushed facies, dry skin, conjunctivitis and congestion of the mucous membranes, and a falling pulse rate with a constant or a rising temperature (*Faget's sign*).

The second phase of the disease, called by some the period of calm, is characterized by cold, clammy skin, bradycardia, hemolytic icterus of the sclerae and skin which may persist into the period of convalescence, a peculiar odor to the skin which has been likened to the fish market or gun washings. There may be subcutaneous effusions which are manifested by deep blue spots or erythematous congestion of the scrotum or vulva. Other findings are melena, hematuria, albuminuria, anuria, oliguria, delirium, nausea, vomiting, torpor, coma, black hemorrhagic vomit which is painless and in some cases projectile. To quote Manson-Bahr, "Everything is congested at the beginning, everything bleeds at the end." Death usually occurs between the 5th and 6th day. *Signs presaging death* are a sudden rise

preparation of the vaccine it being the consensus that such was the cause of the outbreak of jaundice that occurred in 1942–43 among residents of Brazil and American soldiers in the Caribbean areas

One hundred and ninety nine cases of encephalitis have followed vaccinations of 55 000 persons in Brazil It is suggested that some alteration occurred in the virus which rendered the vaccine neurotropic

Special care must be taken to prevent the introduction of yellow fever from endemic to nonendemic areas by infected persons or mosquitoes All ships and airplanes arriving from endemic areas should be subjected to examination and spraying for mosquitoes Unvaccinated persons are kept under the surveillance of government authorities for any unexpired part of the incubation period Those interested are referred to U S Public Health Service Foreign Quarantine Division Circular June 9 1937, subject 'Measures to be observed to prevent introduction of yellow fever into the United States by aircraft

U S Public Health Service Foreign Quarantine Circular No 71 Jan 27 1941, subject 'Quarantine Inspection and Treatment of Aircraft of the Military Forces of the United States

General Measures to Be Used in an Epidemic

The patient should be isolated in a room specially screened with No 18 mesh wire or in a special hospital ward free from mosquitoes, for four days from the onset of symptoms (Period of communicability) The quarters in which the infection may have occurred should be fumigated Those who have probably been exposed should be isolated for ten days in a room protected with a No 18 mesh wire screen for 10 days (period of inoculation) and inspected daily for symptoms All persons should be vaccinated immediately against yellow fever in the A aegypti infected area who have not already received vaccine A daily inspection should be made of the entire military and civilian population in the exposed area in order to discover any early cases of yellow fever An autopsy or viscerotomy should be performed on all cases dying of fever of ten days duration or less both in the military and surrounding civilian population and the tissue from the liver examined for histological evidence of yellow fever A vigorous organized campaign must be instituted to control A aegypti breeding It is a domestic mosquito and breeds mostly in clear water in artificial containers such as cans rain barrels etc Its eggs are resistant to drying The adult forms are found most frequently in human habitations Its flight range is limited to a few hundred yards The use of a 5 per cent solution of DDT as a spray is now our most effective method of ridding houses and buildings of this mosquito Rooms so treated are free of mosquitoes for about 1 month and harbor very few for a long period thereafter

Dengue Fever

Dengue fever is an acute non fatal febrile widely distributed infection of tropical and subtropical regions It is caused by a filtrable virus transmitted by mosquitoes and is characterized by a sharp onset usually with paroxysms of short duration intense headache joint and muscle pains an extreme leucopenia and irregular eruptions The *source of infection* is the blood of infected persons during the first three to five days of the disease It is transmitted by the bite of infected mosquitoes *Aedes aegypti* or *Aedes albopictus* from eleven days after biting a patient until the death of the mosquito

The *incubation period* is from three to fifteen days most often five or six days The period of communicability is from the day before the onset to the fifth day of the disease *Immunity* is inconstant and brief The disease is characteristic for its high case rate spreading almost as rapidly as influenza It is most prevalent after the rainy season in the tropics In temperate climates the disease most often occurs during the summer months and usually in low altitudes near the seacoast or well watered locations It usually ends abruptly after the frosts begin There have been large outbreaks in Georgia Florida, Louisiana Puerto Rico India and Australia It occurs only where the vector Aedes aegypti exists It is common in frequent epidemics in the Philippines When occurring in epidemics in The United States it begins as a rule in the southernmost States and moves north until the range of the vector mosquito is stopped by climatic changes or the season of the year

of temperature, or a sudden fall in temperature *after the eleventh day* Convalescence may follow, however with rapid recovery

In severe cases after the initial phase there may be a secondary rise in temperature accompanied by pronounced jaundice, anuria, black vomit, acute hepatitis stupor, coma and termination in crisis A pronounced albuminuria *and leucopenia are characteristic of yellow* fever

DIAGNOSIS

The diagnosis is not difficult in epidemics and should be suggested when several deaths in a community occur in quick succession preceded by albuminuria and black vomitus The clinical diagnosis usually rests upon the sudden onset, fever, prostration slow pulse in relation to body temperature, severe headache and backache congestion of the mucous membranes bleeding gums black vomitus (especially in severe cases), late jaundice and brief *duration of illness* The diagnosis can be confirmed by identification of the virus in specific protection tests on animals When autopsies are not permitted, the viscerotome is used to obtain specimens from the liver of persons dying less than 10 days after the onset of an acute febrile illness Suspected blood will *retain its infectivity for several weeks if kept in* an ice chest

The following diseases must be excluded *falciparum* malaria, Weil's disease infectious hepatitis, and dengue fever

MORTALITY AND PROGNOSIS

The prognosis is favorable if the initial temperature does not exceed 105°F There have been no deaths reported with a fever under 103°F and no recoveries with fevers going above 106 F In epidemics the mortality has reached 50 per cent It is below 10 per cent in natives of endemic zones of yellow fever

TREATMENT

There is no specific treatment The patient should be at complete rest in bed in a room screened with 18 mesh screen A bed net should be supplied A saline laxative should be given at the outset and enemas thereafter as needed During the acute stage citrus fruit juices and alkaline waters (3000 c c of tap water daily, to which has been added 15 gm *of bicarbonate*) In mild cases, a light high carbohydrate diet but low in fats, may be allowed The fever is controlled by sponging, and ice caps or cold compresses to the head Vomiting is relieved by cracked ice with cocaine hydrochloride 0 016 gm (¼ grain) by mouth, or codeine sulfate 0 032 gm (½ grain) by hypodermic injection If emesis prevents oral feeding, dextrose, 5 per cent in physiological saline, can be given three times daily (intravenously) to which may be added 3 milligrams thiamine chloride, 15 milligrams nicotinic acid amide, and 50 milligrams of ascorbic acid These may be given either with each clysis or separately *by mouth or parenterally* Vitamin K is suggested if hemorrhagic manifestations of the disease are prominent As soon as the patient is able to eat, he may be given a high carbohydrate relatively low protein diet He may have eggs cheese and milk however The diet should be supplemented *daily with 10 gm of Brewer's yeast and* 50,000 units of vitamin A This regimen is continued until the patient is well along the road to recovery Liver and iron are advised for any associated anemia A long period of convalescence is necessary and resumption of activities should be gradual

CONTROL

The most effective method for immediate control of yellow fever is vaccination It is a living strain of virus (17D) which has been attenuated by tissue culture through many generations It is injected into eggs containing *seven day chick embryos* incubated, minced and suspended in yolk fluid and sodium chloride It is then dried and sealed in tubes Prior to its use it is resuspended in saline solution and injected subcutaneously in a single dose of 0 5 c c This vaccine is made at the laboratories of the United States Public Health Service and of the Rockefeller Foundation All military personnel stationed in tropical regions or in areas where yellow fever is endemic or is likely to be introduced should be vaccinated against the disease Also, all personnel ordered to such regions should be vaccinated before departure Vaccination usually confers immunity of several years duration Human serum is not now being used in the

allied to but distinct from yellow fever It is present in the blood for at least twenty four hours before and after the onset of the fever but is no longer detectable forty eight hours thereafter The virus can survive outside the body for sixty hours and it has been preserved for six months in the frozen or lyophilized states

The only proved vector of the disease is a small hairy sandfly *P papatasii* The fly can easily pass through the meshes of mosquito netting but they have feeble powers of flight being limited to about fifty yards in extent and not over one story in height After biting an infected individual the fly does not become infectious for about six or seven days but it retains its infectivity for the extent of its life

The female lays about forty eggs in rubble caves latrines and cracks in damp walls and masonry In about six to nine days the larva appear The life cycle from egg laying to imago takes about one month in tropical climates longer in temperate zones The larva is infected by feeding on the feces of imago or by eating dead adults

CLINICAL FEATURES

The *incubation time* determined by experimental inoculation of the virus varies from forty two hours to six days The onset is acute and is characterized by a severe frontal and retro-orbital headache short chills stiffness of the back and neck particularly in the sacroiliac region rheumatic pains in the joints and extremities not unlike that seen in influenza and photophobia and pain on movement of the eyes The temperature will be found to be elevated 103 -104 F reaching its maximum in from twenty four to thirty six hours Bradycardia is common at the end of the febrile period the heart rate being between 42 and 60 beats per minute The fever continues usually attaining a crisis on the 3rd day and then receding to normal levels on about the 4th or 5th day While the fever may last for nine days two three or four day fevers comprise 85 per cent of cases

Malaise nausea vomiting epistaxis band like pain across the lower thorax and ill defined epigastric pain may be present at the crisis Constipation is common at the onset and diarrhea at the end of the disease The face is characteristically swollen and flushed and the conjunctiva are congested early in the course of the fever Profuse perspiration is common during the course of the disease and precedes defervescence Convalescence may be associated with dizziness weakness and mental depression There may be an erythema of the face and neck with a subcuticular mottling but there is no true rash Vesicular eruptions on the mucous membranes of the palate and pharynx have been reported

The liver and spleen are not palpable There is no lymphadenopathy and the lungs heart and kidneys are normal Increased cerebrospinal fluid pressure has been reported with an increase in albumin and cells but this has not been confirmed by Sabin (12) in subjects with the experimentally induced disease The *prognosis* is excellent and complications are rare

DIAGNOSIS

The diagnosis of phlebotomus fever should be considered when during summer or autumn a group of people present the clinical syndrome of a three or four day fever with a sudden onset headache changes in the leucocytes muscular pains gastrointestinal and nervous symptoms in a region where the Phlebotomus flies are present

Recent work by Sabin and associates is of help in the diagnosis These workers have established that while a true leucopenia may not be present in this disease there is a pronounced relative and absolute reduction in the segmented neutrophils associated with a simultaneous definite relative and absolute increase in the immature neutrophils (staff cells) A leucopenia is more often seen at the end of the fever and during the first two days of the post febrile period On the first day of the fever there is a relative and absolute decrease in the lymphocytes and a relative and sometimes absolute increase in neutrophils due to an increase in the immature cells The number of the lymphocytes returns to normal on the 2nd or 3rd day of the disease and may constitute from 40 to 65 per cent of the total The segmented cells decrease in number while the immature or non filamented cells increase usually outnumbering the segmented cells This changing relationship between the cells

Dengue occurs equally among males and females it is less frequent among the indigenous than among visiting or transient whites in whom the disease commonly occurs The disease is of military importance as in epidemic form, it could incapacitate an army for protracted periods since it is frequently followed by weakness

CLINICAL CHARACTERISTICS

In about half the cases there is an abrupt onset with a chilly sensation malaise and deep flushing of the face While not severe enough to warrant the term 'break bone fever' there is usually severe rheumatic type pain of the lower extremities or fingers as well as headache, backache and severe pain behind the eyes The temperature may rise to from 102 to 106°F and the duration varies It may last only one day and be extended to nine days The pulse rate is slightly accelerated, the skin hot and dry, and there may be nausea and vomiting Disturbances of taste and smell are fairly common After the invasion period of from 2 to 3 days there is a remission of from one to three days during which the pain disappears and the temperature falls to normal for several days Leucopenia usually begins on the second day of the disease and may reach 2000 on the fifth day Degenerative changes are present in the polymorphonuclear leucocytes There is an early shift to the left with an increase in the immature granulocytes

After a period of remission for several days the fever and bone pain return accompanied by a terminal rash a rubeolar eruption commencing on the palm and dorsum of the hands and later on the chest back of the arms and on the thighs They are dusky elevated spots which disappear on pressure and may be evanescent In some cases they remain for several days and may be followed by a furfuraceous desquamation and itching of the palms and soles The terminal rash and the leucopenia are the most important diagnostic criteria and a blood count is of value if taken in time

Service personnel in the Southwest Pacific theater of war who contracted dengue have shown a low blood pressure bradycardia slow recovery from extreme physical and mental depression leucopenia high temperature and electrocardiographic changes such as a widened QRS complex a delay in the PR interval and minor changes in the T waves and RT segments Dengue occurred in the memorable defense of Bataan in the Philippines

The mortality is nil but the convalescence is accompanied by periods of weakness and mental depression No satisfactory method of immunity exists Repeated attacks are common

TREATMENT

There is no specific treatment for dengue fever Rest in bed in a well screened room and symptomatic therapy with liquids and cold applications may help to make the patient comfortable The pain may be relieved by salicylates, or in severe cases, by morphine

Phlebotomus Fever

This disease also called Pappataci fever sandfly fever summer fever and Mediterranean dengue is an acute specific, fever of short duration caused by a filterable virus introduced by the bite of a sandfly Phlebotomus papatasii

GEOGRAPHICAL DISTRIBUTION

Phlebotomus fever is an epidemic disease of sandy waste spaces occurring in subtropical and tropical areas, usually confined to low lying coastal regions of the countries in which epidemics have been studied although it has been observed in the Caucasus and in the Himalayas at altitudes of between 3 000 and 4 000 feet

Epidemics have been reported in the Mediterranean areas the Balkans Egypt Syria, Turkey Palestine Iraq Central Asia Indo China China, the Sudan Ugunda North West India Federated Malay States Java Brazil North Argentina Guatemala Ecuador and Mexico The disease may occur at any time in the tropical zone, in the subtropics it occurs in the summer and early autumn It is of military importance because it has incapacitated large bodies of troops for periods of from one to two weeks

ETIOLOGY

The disease is caused by a filterable virus with the same properties as that of dengue and

perature is cooler than 48 Fahrenheit *Plasmodium malariae* and *Plasmodium ovale* are relatively uncommon and their distribution is irregular

Transmission

The source of the infection is the blood of an infected individual and the mode of transmission is usually by the bite of the infected *Anopheles* mosquito The mosquito is infected by biting an individual suffering from acute or chronic malaria The parasite develops in the body of the mosquito for from 10 to 14 days (21 for the quartan) after which the sporozoites appear in its salivary glands

Native villages sprayed with a 5 per cent solution of DDT have revealed a marked reduction of mosquitoes in dwellings for 26 days A few entered the dwellings at 29 days but few contained blood and about 92 per cent died within 24 hours The disease is also transmitted by the common use of crude makeshift hypodermic syringes (which are usually unsterilized) by drug addicts or in the case of blood transfusion donors with unrecognized malaria transferring their infection to the recipients The *period of communicability* lasts as long as the sexual form of the malaria microorganism exists in the circulating blood in sufficient quantities to infect mosquitoes In untreated cases this may last for months

Clinical Features

The clinical course and severity of malarial infection depends on factors such as the kind of malaria involved whether it was acquired or induced and the area in which the disease was contracted While it is conceded that the human malarial parasites are well defined species it is known that there are definite morphological and physiological differences existing between strains of the same species obtained from different endemic areas of malaria Though variations are very common in the clinical picture a good percentage of cases present symptoms characteristic for the species of the parasite causing the infection

Vivax or *benign tertian* may be latent for six months The premonitory symptoms are a vague aching in the bones headache and lassitude As a rule the symptoms appear about the 8th day following the bite of an infected mosquito The basic clinical symptoms of rigor heat and sweating during a time of the periodic cycle is closely associated with the cycle of development of the organisms in the blood The onset and duration of the paroxysm occur with the rupture of the infected red cells and the liberation of a crop of merozoites into the blood plasma Some believe that the sudden increase in protein are the cause of the paroxysms Others believe that the rise in plasma potassium level may be responsible for the sequence of events Beeson and Hoagland have found that the intravenous administration of 10 c c of a 10 per cent solution of calcium chloride stopped the rigor almost immediately The paroxysms appear every other day but they may appear daily (quotidian) in which case two broods of parasites are present one sporulating on the even day and the second on the odd day The rigor finds the patient complaining of a severe chilly sensation over the entire body It may last for two hours and be accompanied by vomiting cold and blue skin and convulsions especially if the subject is a child The pulse is rapid and small in volume The hot stage follows the chill The temperature gradually mounts the headache increases the respirations become rapid and the pulse full and bounding The temperature may reach 106°F This stage lasts for two hours and the patient soon becomes drenched with perspiration There follows a feeling of relief and the patient becomes drowsy and falls asleep In a few hours he has no complaint except that of weakness The spleen enlarges during the rigor and may be palpable especially in falciparum malaria The chill or ague is typical of the vivax malariae and ovale tertian seldom of the falciparum variety

Ovale tertian is practically symptomless but it may produce clinical symptoms of a subacute appendicitis or rheumatism

Quartan malaria is due to *Plasmodium malariae* infection It has a long incubation period ranging from 18 to 40 days It is characterized by paroxysms occurring every 72 hours The clinical features are much like those of the vivax malaria with the exception that they may be prolonged and the patient is more likely to complain of nervous symp-

during the course of the disease is an important aid to diagnosis

The sedimentation rate may be normal The Hanger cephalin flocculation test is also normal which fact may be of diagnostic significance since it has been shown to be positive in malaria (13) (14) and infective hepatitis (15)

DIFFERENTIAL DIAGNOSIS

The following points are of diagnostic aid in the differential diagnosis of phlebotomus fever

Phlebotomus Fever The fever lasts for from 2 to 4 days There is no lymph adenopathy or rash The disease usually occurs in the summer or autumn A blood study (daily) will reveal a reduction in segmented neutrophils with a simultaneous increase in staff cells The Hanger test is negative The locale may be significant

Dengue Fever This is a 5 6 or 7-day fever and there is usually a secondary rise after the pseudocrisis Lymphadenopathy is common A terminal rash is common

Influenza This is usually a one or two day fever and occurs in the winter months The *WBC* is normal or increased The increase of immature neutrophils is never accompanied by a pronounced reduction in the segmented cells

Malaria The paroxysms of fever may be characteristic A blood smear may reveal the parasites, and relief follow specific therapy There is no leucopenia The Hanger test is positive

Infective Hepatitis The Hanger test is positive in the icteric stage

Typhus Fever The fever is similar for the first few days There is no lymphadenopathy but the rash is characteristic There is greater prostration in typhus than in phlebotomus fever

Yellow Fever The temperature curve is characteristic There is increasing amounts daily of albumin in the urine Jaundice is present

TREATMENT

There is no specific treatment other than symptomatic therapy This consists of rest in bed saline cathartics at the beginning of the attack when constipation is present aspirin for joint pain and headaches, and bismuth sub carbonate for the terminal diarrhea A liquid or semi fluid diet is recommended during the acute phase of the disease

PROPHYLAXIS

Sleeping quarters should be on high, open dry and sandy ground and a current of air provided by an electric fan if no breeze is present *Dimethylphthalate* and *pyrethrum vanishing cream* are two satisfactory repellants and can be applied directly to the skin Sleeping nets of mesh 45 to the inch should be used when necessary Locations known to harbor the flies should be avoided Cracks and crevices in the walls or earth should be filled, or if this is not possible sprayed with DDT, crude oil or creosote preparations

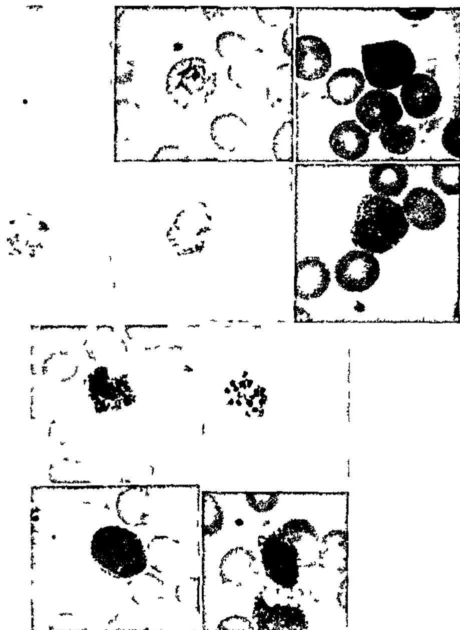
Diseases Caused by Blood Protozoa

MALARIA

Malaria is an acute infectious disease induced by the bite of certain anopheline mosquitoes which are infected with a protozoan parasite the *Plasmodium* It is a protean disease and like syphilis can simulate any disease *One should put aside the text book* idea that chills and periodic fevers are characteristic symptoms of malaria There are four species of plasmodium known to be responsible for the disease in man They are *Plasmodium vivax* (vivax malaria benign tertian malaria or tertian malaria), *Plasmodium malariae* (quartan malaria), *Plasmodium falciparum* (falciparum malaria malignant tertian sub tertian or estivo-autumnal malaria) and *Plasmodium ovale* which produces a mild illness similar to vivax malaria

Geographic Distribution

The distribution of malaria is world wide, but that of the different species of parasite varies *Plasmodium vivax which is most* widely distributed, occurs between 45° N and 45° S latitude, it is the most common species found in the temperate zone *Plasmodium falciparum* is usually confined to the tropics and subtropics In many tropical regions it is the most common species It rarely occurs when the average summer temperature is lower than 70 Fahrenheit or the winter tem



(*Courtesy Aimee Wilcox National Institute of Health*)

Fig 155 Photographic Reproductions of Stages of *P vivax*

Top row left to right Young trophozoite —Trophozoite of moderate size Enlargement of cell and Schuffner stippling evident —Still older trophozoite showing pseudopodial process

Second row left to right Mature trophozoite with irregular outline —Schizont showing initial division of chromatin —Older schizont showing four divisions of chromatin

Third row left to right Still older schizont —Mature schizont with about 16 divisions of chromatin and some clumped pigment

Fourth row left to right Macrogametocyte —Microgametocyte near a presegmenting schizont

through a lack of facilities or of skill and technique in detecting the plasmodia in the blood films If the practitioner does not want to take the time to develop his skill in the identification of the blood smears he should at least know how to prepare a satisfactory film for

toms There is a feeling of illness between paroxysms not present in vivax malaria Fever may occur on two successive days if there are mixed broods of parasites

Falciparum malaria is the most severe type It has a tendency to involve the internal organs and thus simulate almost any disease The incubation period is 10 to 12 days On account of the tendency to infection with more than one generation and irregular segmentation the temperature curve of this type of malaria is usually irregular or remittent The paroxysms may last for 20 hours and the intercurrence of approaching and receding paroxysms may result in an almost continuous fever Many cases are brought into hospital in coma because of cerebral involvement with *P falciparum* In the *gastrointestinal* or *bilious'* type the symptoms may resemble typhoid fever or yellow fever There is usually *high fever vomiting and enlarged painful* spleen and liver with icterus There is a *cerebral type* in which the patient is usually in coma when first seen the temperature may reach 108°F and unless immediate intravenous therapy is instituted death may result The mortality in most of these cases is high despite treatment There may be delirium, mania epileptiform convulsions, cerebral paralysis psychic disturbances hemiplegia aphasia and bulbar symptoms The coma may persist for from 12 to 20 hours The pulse is rapid and pounding the skin hot and dry If consciousness returns, a subsequent attack may be fatal Falciparum malaria is especially severe in children

Atypical Types of Malaria

The following *atypical types* have been described

1 *Cerebral Type* This form simulates heat stroke acute mania acute alcoholic psychoses or afebrile psychoses Headache and prostration are prominent and all symptoms are relieved on anti malarial therapy
2 *Visual Type* Symptoms are dimness and clouding of vision with headaches of long duration temporal or frontal in location
3 *Neurological* A malarial basilar meningitis may cause involvement of either the optic or the eighth nerve There may be only nausea and vomiting in children
4 *Endocrine Type* Malaria may cause damage to the adrenal or thyroid gland with resultant symptoms of glandular deficiency In these, substitution therapy has proven beneficial
5 *Pulmonary Type* Emboli discharged into the pulmonary circulation may occur resulting in cough asthma and other pulmonary symptoms but with negative physical findings Antimalarial therapy has given rapid symptomatic relief
6 *Cardiac Type* There may be acute heart failure resembling cardiac disease or anasarca resembling wet beriberi Shortness of breath exertional dyspnea weakness, and tachycardia may be the only symptoms present
7 *Gastrointestinal* This form may resemble cholera with profuse diarrhea and collapse, or there may be blood and mucus in the stools suggesting bacillary dysentery Pain may be complained of over the gallbladder resembling acute cholecystitis Biliary malaria is suggested by slight jaundice Deep jaundice may resemble yellow fever, Weil's disease or infective jaundice
8 *Nephritic Type* This may resemble acute nephritis with casts in the urine The initial symptoms may be frequency of urination or a brown black or red discoloration of the urine The initial complaint may be anuria which is present in acute malarial nephritis as well as in the terminal stage of blackwater fever
9 *Hemorrhagic* Purpura may be seen from intradermal hemorrhage

A review of the above atypical forms shows that we should give up our old ideas that chills and periodic fevers are constant symptoms of malaria and that their absence *should not* rule out its occurrence in those who are living or who have lived at some time in the tropics or endemic areas of malaria

The Laboratory Diagnosis of Malaria

The diagnosis of malaria is entirely dependent upon finding and identifying the parasites in the blood Too often the clinician and general practitioner omit this procedure, either



(*Courtesy Aimee Wilcox National Institute of Health*)

Fig 155 Photographic Reproductions of Stages of *P vivax*

Top row left to right Young trophozoite —Trophozoite of moderate size Enlargement of cell and Schuffner stippling evident —Still older trophozoite showing pseudopodial process

Second row left to right Mature trophozoite with irregular outline —Schizont showing initial division of chromatin —Older schizont showing four divisions of chromatin

Third row left to right Still older schizont —Mature schizont with about 16 divisions of chromatin and some clumped pigment

Fourth row left to right Macrogametocyte —Microgametocyte near a presegmenting schizont

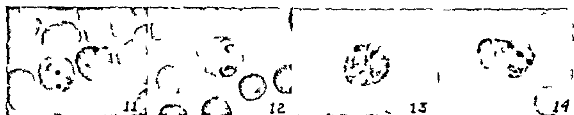
through a lack of facilities or of skill and technique in detecting the plasmodia in the blood films If the practitioner does not want to take the time to develop his skill in the identification of the blood smears he should at least know how to prepare a satisfactory film for

shipment to a state laboratory or medical school, where the proper techniques and examinations can be carried out

The *thin film* is satisfactory for the study of the various species of malaria when the *infection is so heavy that the parasites can be* found without a tedious search It also shows the accompanying blood picture One must know *the identification of the different species* of plasmodia in their various stages in the thin film before attempting to identify them in a thick film In light infections the thin film may fail to reveal a small percentage of positive cases

The *thick film* is a method of concentration numbers of slides can be dehemoglobinized and stained at one time it is particularly well adapted to surveys *on given populations* and to the use of State laboratories where large numbers of slides for malaria examination are received daily during the summer and fall it gives an idea of the degree of infection and can be a great *help* because of the increased density of parasites in identifying the type of malaria in cases where only one or two young forms can be found in the thin film It gives a fairly good idea of the number of leukocytes and shows pigmented white cells more readily than the thin film

In nearly all cases parasites will be found in thick films from patients who show active symptoms of malaria Parasites may be reduced however to a microscopically undetectable level by anti malarial drugs Also in persons with extreme susceptibility symptoms may occur before parasites can be found



(Courtesy Aimee Wilcox)

Fig 156 Cells Showing Double Infection with P vivax

11 Two cells each containing two young trophozoites
12 Enlarged cell containing two slightly ameboid young trophozoites
13 Schuffner s stippling quite apparent in cell infected with two medium grown trophozoites
14 *Double infection of a cell by a presegmenting schizont and another old parasite—apparently* a macrogametocyte

It is advantageous for the discovery of a lower concentration of parasites, and saves time in the examination The technique is simple A large drop of blood is placed on a clean slide and, with the corner of another slide a needle or other instrument the drop is spread so that the red corpuscles are several layers thick in the center tapering off to a single layer at the margin The film is allowed to dry flat one should then be able to read print through its thickest part Before staining the film should *be placed in an incubator at 37°C for one hour* or kept at room temperature overnight The slide should not be heated in any way and should be stained within forty eight hours, because of the degenerative changes that take place

To quote Wilcox whose excellent monograph on malarial diagnosis should be read by all who are interested (5)

> Because of its efficiency in picking up cases with rare parasites it gives a much more accurate idea of the incidence of malaria in a survey and because great

> In these latter cases examination of subsequent smears should be made on successive days '

> The thick film can be used for examination of the blood for trypanosomes filaria the spirochetes of relapsing fever and for the estimation of the percentage of eosinophils

Mixed Infections Wilcox (6) has pointed out that it seems to be the tendency in mixed infections for one species to predominate over another Also one should not overlook the possibility of finding numbers of one species in a film and yet completely missing the rare parasite of another species *Typical and characteristic forms of the respective species must be found in order to determine a mixed infection* In thin films, these distinctive forms *in aestivo*-autumnal (*P falciparum*) malaria are the crescent shaped gametocytes In benign tertian (*P vivax*) *they are the large* ameboid trophozoites, or any stage of the parasite in an enlarged cell containing Schuffner s stippling In quartan malaria (P *malariae*) they are the pigmented band forms or any heavily pig



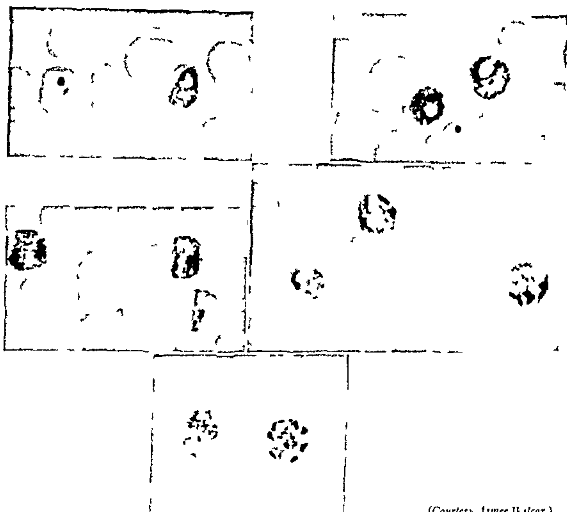
Photographic Reproductions of Stages of *P falciparum* (*Courtesy Aimee Wilcox*)

Fig 157 Upper row left to right Macrogametocyte at top two macrogametocytes lower down —Heavy infection of ring form trophozoites often found in fresh infections of estivo autumnal malaria showing double chromatin dots double infection of the cell marginal forms and signet ring forms

Lower row left to right Heavy infection from a moribund case of estivo autumnal malaria note variations in size of trophozoites and number of multiple infected cells —Mature schizont from same case

(*Courtesy Aimee Wilcox*)

Fig 158 Thick Films of *P falciparum* Left to right Heavy infection ring stage trophozoites—Young trophozoites and gametocytes The background is clouded with remains of young cells



(*Courtesy Aimee Wilcox*)

Fig 159 Photographic Reproductions of Stages of *P malariae*

Top row left to right Young ring form trophozoite and medium grown trophozoite—One ring form with slight pseudopodial process and two older trophozoites each with elongated chromatin mass and profuse heavy pigment

Middle row left to right The band form parasites the one on the left showing two divisions of chromatin the other two being different stages of trophozoites—Reading from the left medium grown trophozoites two presegmenting schizonts—one with four the other with three divisions of chromatin

Bottom row A large trophozoite and a mature schizont

mented form beyond the ring stage in an unenlarged cell

In malaria the total number of white cells is usually below normal Certain factors such as pneumonia or the febrile phase of malaria may alter this picture and the count may rise In the thin film there may be the picture of secondary anemia Clumps of malaria pigment in the white cells are almost certain proof of malaria, and usually upon close inspection one will find plenty of parasites as well

The Treatment of Malaria (7)

Available evidence indicates that *atabrine* is as effective or more so than *quinine* both in suppressive use and in the treatment of clinical attacks The plasma level of the drug is fundamental in determining its efficacy Under ordinary conditions the rate of absorption of the two drugs is not significantly different In the usual dosage however quinine reaches an effective plasma level more rapidly than does atabrine In order to attain effective concentrations of atabrine in the plasma it is necessary to give relatively large initial doses or wait for a varying period while the drug accumulates Since a great many plans of giving atabrine and quinine have been tested little can be gained by modifications which serve only to confuse the problem

As a rule there are fewer relapses following atabrine treatment than quinine therapy although the difference is not great The tendency of patients to relapse after quinine treatment is characteristic It must be remembered that *atabrine* has no effect on the gametocytes of *P falciparum* and as a result patients with this type of malaria must later be treated with *plasmochin* Plasmochin has no value for the treatment of clinical malaria according to many authors It does have a definite effect upon the gametocytes of the malarial parasite being especially effective against those of *P falciparum* For this reason the drug is usually given following a course of atabrine or quinine to prevent the transmission of falciparum malaria It has not been established that the use of plasmochin constitutes a practical method of malarial control It has been stated that the incidence of relapses is less when plasmochin is given after atabrine or in conjunction with quinine This is controversial and this claim has not been borne out by recent experience

Untoward Effects of Atabrine, Quinine, and Plasmochin Each of the above mentioned drugs is capable of producing toxic reactions Mild disagreeable reactions from atabrine may occur in certain patients given the drug for suppressive treatment As a rule the reaction follows one of the first few doses and is more likely to occur when atabrine is given between meals They consist of nausea abdominal cramps or occasionally headache, vomiting and diarrhea They can be prevented in most cases by giving sodium bicarbonate or sweetened drinks such as tea with the drug They are never serious and disappear invariably if the drug is continued About one third of patients taking atabrine develop a yellow discoloration of the skin It does not represent hepatic damage is not dangerous and is not an indication for discontinuing the drug Extensive studies have failed to show that atabrine in the usual doses has any effect whatever on the flying capacities of air force personnel It has been taken by large groups for a year or more without any lasting untoward effect having been observed

The symptoms following the administration of *quinine* in therapeutic doses are tinnitus impairment of hearing dizziness tremor and palpitation They have been used as an index that the drug is being absorbed and is exerting an effect In milder degrees some of these symptoms may be seen during suppressive treatment Some aviators have found them troublesome The more severe effects are usually the result of individual hypersensitivity

The margin of safety between therapeutic and toxic doses of *plasmochin* is small The toxic symptoms include abdominal pain nausea vomiting cyanosis headache dizziness and drowsiness hemoglobinuria jaundice and acute yellow atrophy of the liver are rarer but very dangerous effects

Conservation of Quinine While the first total synthesis of quinine identical in every respect with the natural product from cinchona bark has been accomplished due to the present shortage of available quinine its use should be restricted to

1 Severe infections with *P falciparum* in which intravenous therapy is deemed essential
2 Serious intolerance to atabrine
3 When atabrine is not available

TABLE LI

Differentiation of Malarial Parasites on Stained Thin Films

(After Wilcox)

	Plasmodium vivax	Plasmodium malariae	Plasmodium falciparum	Plasmodium ovale
Infected Cell	Larger than normal, pale, often bizarre in shape. Schüffner's dots very often present. Multiple infection of erythrocyte not uncommon	About normal or slightly smaller. Sometimes darker in early stages. Ziemann's dots rarely seen. Multiple infection of erythrocyte rare	Normal in size. Multiple infection of erythrocytes more common than in the other species. Maurer's dots sometimes seen (in overstained smears or when pH of water is on the alkaline side)	Somewhat larger than normal, often with fringed or irregular edge and oval in shape. Schüffner's dots appear even with younger stages than in vivax, more readily and more deeply than in vivax
Small Trophozoite (Early Rings)	Signet ring form with heavy chromatin dot and large cytoplasm, [illegible] possibly with fine pseudopodia	Signet ring form with heavy chromatin dot and heavy plasma ring which is often smaller, thicker [illegible] than that of vivax	Small thread-like cytoplasmic circle and one or two small chromatin dots (Double chromatin dots more frequent than in other species). Marginal and bridge forms are frequent. May disappear in this stage from peripheral circulation and return to internal organs for development	Small, darker in color and more solid as a rule than those of falciparum. Schüffner's dots regularly present in almost 100% of infected cells
Growing Trophozoite	Same as above with gradual increase in amount of cytoplasm and chromatin. Often with more distinct pseudopodial processes. Small yellowish brown pigment granules in cytoplasm, number increasing with growth of the parasite	Chromatin rounded or elongated; cytoplasm is a compact form with little or no ameboid, or in a narrow band form across the cell. Dark brown pigment granules—may have peripheral arrangement	This stage remains in the ring form but chromatin and cytoplasm increase to the extent that in size the parasite resembles closely the small trophozoite of vivax. A few pigment granules give a yellowish tinge to the cytoplasm. This is usually the oldest asexual stage seen in the peripheral circulation	Resembles closely same stage of *P. malariae* but is considerably larger
Large Trophozoite	One abundant mass of chromatin, loose, irregular cytoplasm with [illegible] ameboid [illegible] off; nebulous pigment. Parasite practically fills enlarged cell by end of 36 to 40 hours	One mass of chromatin, often elongated, frequently less definite in outline than that of vivax. Cytoplasm dense and compact with few irregularities of outline, round to oblong, or sometimes band shape. Pigment granules larger, darker than in vivax, with a tendency toward peripheral arrangement. Fills or almost fills normal cell	Stages seldom seen in peripheral blood. Very small, solid with one small mass of chromatin. Lightly staining compact cytoplasm and with a haze of pigment scattered through the cytoplasm or with very dark pigment collected into one small dense block	Pigment is lighter in color and is less conspicuous
Schizont (Presegmenting)	Chromatin divided into a number of masses; cytoplasm shows beginnings of separation into strands; pigment shows tendency to collect in part of the parasite	Same as vivax except that the parasite is smaller, the divisions of chromatin masses approaches segmentation, and more delayed clumping of pigment	When found in peripheral blood this stage resembles the same stage of *P. malariae* but is smaller and the pigment is likely to be completely clumped in one small dark mass	About 25 per cent of infected cells are definitely oval shape. Usual picture is that of a round parasite in center of an oval cell. Many cells with indefinite fringed outline. Pigment lighter in color and less coarse than in *P. malariae*
Mature (Schizont)	12 to 24 divided forms or merozoites, composed of a central dot of chromatin and a portion of cytoplasm. The pigment is in one or two clumps. Parasite practically fills enlarged cell	6 to 12, usually 8 or 10, merozoites in a rosette or irregular cluster. Practically fills normal cell	8 to 24 merozoites which are very small compared to those of other species. Rarely found in the peripheral blood. Fills two-thirds of normal red cell	Usually 8 merozoites arranged around a central block of pigment

TABLF LI—*Continued*

M g m tocyte	Dark bl hom g u cytopl sm ith n a u l s small mpa t d rk red ually nt h m t n b d t da k b n p gm t tt r d th gh yt pl sm Wh n ow u u lly fll o ly ill nl g d c ll The tl s tcula o d a d gul r	Cyt pla m a d ch omat n s me s ax Pigment s b nd t d k brown a s r tl n n ax Wh n g own u ally flls the normal ed ll O tline ircular or d	Cyt pla m pos bly l r r bl e than i m r g met yt U u lly s ngl d k ed chr mat m sn arc nt ras oc at d with co c nt at d aggregat o of pigm t dark than i mi ogam tocyte Cres nt c o a ag shap d al t lf t m s d r t r f eryth yte le gth po s bly l ger and m l nd r tl a m c ogameto yte	D st ngu l d from P m la ae by s e f f cte l s a d by Schüffner s dots Le s ea y to d ffe nt at fr m iva S ld m o c er ta n d in an oval ythr cyte
M g m t yte	L ght bl g y p k lm t lo le s yt pl m l ge d ff se l ght ed p k h m t — lly e tr lly pl d f t w th l a aro d hr mat n m s Ab nd nt yell w h b wn p g m tma thr ugho t yt pl m When g ow b ut tl e f a mal cell U u lly l r tl ne	S m a a e pt s x Whe g o n hll o alm t fll n rmal d ll	Ofte the cyt pl m s p ler th n in m c o-gameto yte—g ay sh blue r p k Lo s d ff s l ght ta n g g ules r th ads l ch omat s att ed tl nume o s gran l of p gm t th ghout cent l half o m e fpa a t Pa a te pos bly b ler t t r a d w th mo e r u d d en ls tl an tl s of mac ogameto yt	
L ngth of Ase u l Cy le	48 ho s	7 h u	48 h u	48 ho s
S ges i P ph er l Bl d	All	All	Ls ally g fo m t pho o tes a d g met cyt s Oth st g s rar ly fo nd exc pt n e tre s s	All
R ma ks	M tage of g wth l k ytob s n o f lm than oth r sp c es G m to yt s app ar arly in ycle	Pa a t a e u u lly m c mpa t rd hence pl ear m e nte ly ta ned th n th se of oth r omm n pe i Cam to ytes ra er than n th r spe es app r lat Lea t ofte f nd of thr e ies the U S	Pa a t s f qu tly mo e num u tha n oth l tt n Unl ke th pe es— g wth l a al form f ll ng the r g stag take pla i te al ga s	Spe l ot f u d to date in Un ted St t D ff ent at on n t poss ble n th ck film

4 *Following repeated relapses in spite of atabrine*

Suppressive Treatment Drug suppressive treatment is an emergency procedure which should be employed only when personnel must travel in an area where there is a substantial risk of malaria and where protection from mosquitoes is impossible There is no known drug *which in safe doses will prevent mosquito borne* infection Atabrine however if taken regularly in proper doses will suppress clinical *symptoms for varying periods of time and* enable men to remain active in spite of infection which otherwise would incapacitate them After they return to sanitary areas suppressive treatment should be discontinued as soon as is feasible

To be effective the drug must be taken regularly In order to be sure that this is done a record should be made of each dose

Suppressive treatment should be instituted as soon as possible after arrival in an uncon*trolled malarial area There are advantages* however, in starting it in advance of exposure People become disciplined in the routine of taking the drug and disagreeable reactions are experienced before they reach their destination The institution of treatment two weeks in advance of exposure may be advantageous in that a high plasma level of the drug is achieved by the time clinical symptoms might be expected to appear However when men must travel to their destination by boat seasickness may be a contraindication to the institution of atabrine *in the period preceding arrival in the* malarial area

After suppressive treatment has been discontinued most of the men who have been infected develop clinical malaria (the majority within *two or three weeks) and will then* require clinical treatment Consequently suppressive treatment should not be stopped until the men have returned to a base where adequate medical care is available

In highly malarial regions under the stress of combat suppressive treatment may fail to prevent a break through of clinical symptoms These cases should be given a course of clinical treatment

Suppressive Regime

1 Atabrine 0 1 gm ($1\frac{1}{2}$ grains or 1 tablet) should be given once daily at the evening *meal for six days each week (Total 0 6* gm per week)

2 An alternative method is to give atabrine 0 05 gm ($\frac{3}{4}$ grain or one half tablet) once daily at the evening meal for six days each week and a dose of 0 1 gm ($1\frac{1}{2}$ grains or one tablet) at the evening meal of the seventh day (Total of 0 4 gm per week)

3 Quinine should not be used except in a few cases when indicated The dose *recommended is 0 6 gm (10 grains) of* quinine sulfate daily at the evening meal

4 Plasmochin is not used at any time, for suppressive treatment

Management of Clinical Attacks of Malaria

a *Diagnosis* (1) Malaria should be suspected not only in patients with periodic chills and fever, but also in any obscure illness febrile or non febrile, in endemic regions The symptoms are many and varied

(2) The diagnosis must be based on the *actual finding of parasites in the blood* The blood should be examined as soon as possible and preferably in thick smears in order to concentrate the parasites Each smear should be examined carefully at least five minutes before pronouncing it negative Thin smears should also be made for use when a species diagnosis cannot be made from thick smears, each should be examined for at least fifteen minutes In *P falciparum* infections, the proportion of infected erythrocytes should be estimated when 5 per cent or more erythrocytes are *infected treatment should be as for a comatose* patient If parasites are not found smears should be made on successive days because the symptoms in a first attack may appear when the density of parasites is low and because *in P falciparum infections there may be* very few parasites in the circulating blood during the second twenty four hours of each asexual cycle

(3) Even in severe *P falciparum* infections with cerebral symptoms including coma it may be difficult to demonstrate parasites In every case of febrile illness in which coma or shock occurs in a patient in or from an endemic area *P falciparum* malaria should be suspected Excessive fatigue headache and fever are frequently the only prodromal symptoms of cerebral malaria This form may simulate

acute alcoholism, or the patient may be maniacal and require morphine During the stage of onset the temperature is often little elevated and in the presence of coma it may be normal or subnormal If the facilities for immediate examination of blood smears are not available, malarial therapy should be immediately instituted in such emergency cases

(4) When treatment is started before parasites can be demonstrated it should not be continued beyond a period of one week unless the diagnosis is confirmed by finding the parasite It is rare for the fever of malaria not to respond to adequate doses of *atabrine* or *quinine*

b *Uncomplicated Malaria—The Patient Is Able To Retain Oral Medication* If the diagnosis has been confirmed patients who are seriously ill and do not respond to oral therapy should receive intramuscular or intravenous therapy (as described later) until a therapeutic response has been obtained In occasional cases especially in *P falciparum* infection in which fever is persistent method (1) or (2) should be continued beyond the period of seven days at the discretion of the medical officer

(1) The best method is to give atabrine alone in relatively large initial doses followed by smaller maintenance doses Recommended dosage *atabrine hydrochloride* 0 2 gm (3 grains) and sodium bicarbonate 1 gm (15 grains) by mouth with 200 to 300 cc of water (or an equal amount of sweetened tea or fruit juice) every six hours for five doses followed by 0 1 gm ($1\frac{1}{2}$ grains) three times daily after meals for six days (total 2 8 gm in seven days)

(2) If atabrine is not available use quinine alone as follows *quinine sulfate* 1 gm (15 grains) by mouth three times daily after meals for two days followed by 0 6 gm (10 grains) three times daily after meals for five days (total 16 gm in seven days)

(3) *Plasmochin* may be given in connection with either of the foregoing treatments however its routine use is not advised If *plasmochin* is given the patient must be hospitalized and closely watched *Plasmochin* may be given immediately following atabrine (*not with it*) or in conjunction with quinine on the last days of treatment with that drug The course consists of plasmochin 0 01 gm ($\frac{1}{6}$ grain) by mouth three times a day after meals for four days except for debilitated patients, who should receive only two doses daily Each dose of plasmochin should be accompanied by at least 1 gm (15 grains) of sodium bicarbonate The fluid and sugar intake should be liberal during and for some days after the course *Plasmochin* should be discontinued at once if any toxic symptoms appear

The Combined or QAP Treatment The combined or QAP treatment has been used in India by Amy and Boyd (8) as well as by the British Army It has been endorsed by the Subcommittee on Tropical Diseases of the National Research Council (9) It is now considered the best treatment for acute malaria

Quinine sulfate or *totaquine* (0 64 gm or 10 grains) is given three times daily for two or three days owing to its more rapid action in controlling the pyrexia and multiplication of the parasites *Atabrine* (0 1 gm or $1\frac{1}{2}$ grains) is then given three times daily after meals for five days After a rest period of two days *plasmochin* (0 01 gm or $\frac{1}{6}$ grain) is given three times daily after meals for five days

c *Severe Malaria or Malaria Complicated by Vomiting Coma or Other Serious Disorder* (1) General measures are instituted to control vomiting Solid food is withheld just before a paroxysm is expected Sips of alkaline water may be helpful If emesis is frequent the intravenous administration of 5 per cent dextrose in isotonic solution of sodium chloride is indicated as many patients who vomit become dehydrated and develop acidosis From 200 to 400 c c may be injected by the usual technique this injection may be repeated if necessary or larger amounts may be given by the continuous drip method at the rate of 50 drops per minute The dextrose should be supplemented by 1 mg of thiamine hydrochloride for each 25 gm of dextrose

(2) Coma may be present or imminent in cases of *P falciparum* infection even though parasites are not found in the blood smear This condition constitutes a grave emergency On reasonable suspicion of the diagnosis parenteral treatment must be immediately instituted The intravenous administration of quinine is preferable in the light of present

knowledge but it is possible that the intramuscular injection of atabrine is equally effective

Parenteral Therapy

1 *Atabrine dihydrochloride* 0 2 gm (3 grains) in 5 c c of sterile distilled water injected intramuscularly with the usual precautions into each buttock (total 0 4 gm or 6 grains) If necessary, one or two additional doses of 0 2 gm (3 gr) may be given intramuscularly at intervals of six to eight hours As soon as the patient can take and retain oral medication atabrine should be given by mouth and intramuscularly, the dose by both routes totalling 1 0 gm in forty eight hours, followed by 0 1 gm three times a day after meals for five days (total 2 8 gm in seven days)

2 *Quinine dihydrochloride* 0 6 gm (10 grains) in sterile isotonic solution of sodium chloride 300 to 400 c c (minimum 200 c c), given intravenously with the usual precautions avoiding, especially, too rapid injection If necessary there should be no hesitation to cut down on the vein This treatment may be repeated in from six to eight hours if the situation demands it When the patient can take and retain oral medication a complete course of atabrine (preferable) or quinine should be given by mouth as described for uncomplicated cases

d *General Care* The patient should be maintained at complete rest in bed The fluid intake should be kept at 3 or 4 liters per twenty four hours using the parenteral route if necessary A dangerous effect of a malarial paroxysm is the marked depression in blood pressure which falls to a minimum shortly after the onset of the sweating stage It is possible for such a patient to progress into circulatory collapse resulting from the combined effects of vasodilatation and loss of extracellular fluid This lost fluid should be replaced by salt and fluids judiciously administered Thirst is the best guide to the estimation of the total amount of fluid needed In the majority of cases a fairly normal extracellular fluid balance should be maintained if the patient is allowed to drink as desired a solution containing about 3 0 Gm of salt per liter *Chills* are relieved by hot water bottles and blankets *High fever* is relieved by cold sponges and packs Avoid antipyretics Sedation with the barbiturates may be necessary If the case is one of P falciparum observe the patient closely for signs of cerebral or circulatory collapse Patients with clinical malaria or parasitemia should be screened in special wards or under mosquito nets Care should be taken that they do not sleep against the nets In convalescence a generous high vitamin diet supplemented with ferrous sulfate 0 6 gm (10 grains) three times daily after meals for two weeks should be given

Relapses in Malaria The diagnosis of late relapses is often difficult As long as a patient remains in an endemic area the distinction between reinfection and relapse is practically impossible Relapses should be suspected in all patients who have a history of malaria Exposure strenuous activity alcoholic indulgence trauma, surgical procedures, and travel to a cold climate frequently precipitate serious recurrences If fever occurs under these circumstances or without other explanation in persons in or from endemic areas malaria should be suspected If facilities for blood examination are not available, treatment should be instituted without delay It is desirable, however to prove the diagnosis, especially when relapses are suspected after a long interval In a certain proportion of latent cases, the subcutaneous injection of 0 5 c c of 1 1000 solution of epinephrine enables one to find parasites in the peripheral blood when otherwise they would not be seen In suitable cases this method may be tried Efforts to bring out parasitemia or to precipitate relapses in large groups of men who are symptom free are inadvisable

Treatment In general the treatment for relapses should be the same as that for the initial attack Prolongation of maintenance doses of atabrine to a total period of two or three weeks may be tried In cases of repeated relapses in spite of atabrine therapy the quinine treatment mentioned under uncomplicated malaria (paragraph (2)) may be used and continued with a daily dose of 0 6 gm (10 grains) to a total period of three to four weeks

BLACKWATER FEVER

Blackwater fever occurs mostly in sensitized individuals, such as those who have lived for long periods in endemic areas of malaria and subject to frequent infections with the falciparum parasite Rarely does it follow a primary attack of malaria *Precipitating factors* are chilling trauma, alcoholism fatigue exertion and excessive amounts of quinine The three cardinal *symptoms* are (1) hemoglobinuria, (2) fever, and (3) icterus

Clinical Features

The onset is accompanied by an elevation of temperature which may reach 102–105 F There may be chills Other symptoms are an enlarged painful spleen bile stained vomiting which may be persistent abdominal pain jaundice or icteric sclerae hepatomegaly severe prostration, progressive severe anemia elevated plasma bilirubin with an increased indirect Van den Burgh reaction which may become direct later There is usually some degree of urinary suppression on the 8th day or later The color of the urine varies from light red to black (hemoglobinuria) Asexual forms of *P falciparum* are usually absent from the peripheral blood within from 2 to 3 hours of the onset Crescent forms and tertian and quartan varieties may be present Death may occur from convulsions coma or complications such as pneumonia or septicemia One attack predisposes to another and the third may be fatal The death rate varies from 25 to 50 per cent Blackwater fever is not infrequent in malaria infected patients returning from the tropics to temperate climates and it is especially dangerous in pregnant women As a rule death is the result of anoxemia cardiac failure anuria or pernicious vomiting The urinary suppression is due to the precipitation of acid hematin in the renal tubules

Treatment

Atabrine or quinine should not be given until convalescence from the attack of blackwater fever has been established The patient should be kept strictly at rest in bed and treated as if for shock A minimum of 2 000 c c of fluids should be given daily or more if possible and vomiting is not too severe During the period of vomiting if the urine is acid or anuria exists 1000 c c of saline solution or 5 per cent dextrose solution should be administered intravenously If the urine remains acid this should be repeated after twelve hours After the vomiting has been controlled give sodium bicarbonate 0 6 gm (10 grains) orally every 1 to 2 hours until the urine becomes alkaline to litmus paper and thereafter only if the urine becomes acid When the patient is unable to void urine, he should be catheterized every four hours in order to determine the litmus reaction and the amount of output. For severe anemia transfusions should be given and repeated daily as needed After convalescence has been established if plasmodia are present in the blood give *atabrine* 0 1 gm three times daily for from 5 to 7 days Watch for a recurrence of hemoglobinuria, as atabrine has occasionally precipitated an attack *Caffeine citrate* is advised for diuresis, the dosage being 5 grains three times daily

These patients should be advised to not return to the tropics They should be given liver injections and iron therapy by mouth as after treatment, and when possible sent to a temperate zone Some of these cases can be prevented by carrying every case of falciparum malaria to a complete cure

African Trypanosomiasis (Sleeping Sickness)

Trypanosomiasis is a disease caused by the bite of the tsetse fly the *Glossina palpalis* or the *Glossina morsitans* which are the intermediate hosts of certain protozoal parasites belonging to the class known as trypanosomes The disease follows the invasion of the blood stream either by the *Trypanosome gambiense* or *rhodesiense* transmitted to man by the vectors the tsetse flies either from a human case of the disease or from reservoirs in wild animals The *incubation time* in man is about two weeks In its normal course the disease passes first through a stage in the circulatory system then through a stage in the lymphatic system and finally through one in the central nervous system These stages usually overlap and each may last for several months The average duration of the disease is one year terminating fatally if not treated early

GEOGRAPHIC DISTRIBUTION

Up to twenty years ago, trypanosomiasis has been limited mainly to the African continent, from where it has been carried in recent years to all the Old World centers of commerce It has never found a suitable vector in the New World However, there is a possibility that the tsetse fly may be carried alive across the waters separating our continent from Africa Dead tsetse flies, killed as a result of careful spraying and fumigation, have already been found on inspection of some of our large ferry service planes

DIAGNOSIS

Kellersberger has stated that any individual exhibiting suspicious symptoms who has had either direct or indirect contact with tropical or subtropical Africa must at least be considered as a suspicious case (10) These patients may linger on undiagnosed for months and years and upon returning to temperate climates where their resistance can be built up they may present only an indefinite picture of general ill health When the former residence has been ignored it is extremely unlikely that a correct diagnosis will be made

The *symptoms* that should arouse suspicion are (1) persistent headache (2) a light body rash (3) miscarriage in women (4) edema (5) painful sensations and (6) psychoses and mania followed by somnolence and death Those who have seen many of these cases can diagnose them by the manner in which the patient walks and sits by the characteristic dull listless, facial expression or the lusterless appearance of his eyes

Any patient returning from an endemic area manifesting irregular or intermittent fevers and who is resistant to antimalarial therapy should be considered a possible case of sleeping sickness The blood should be examined for trypanosome A thick drop of blood is stained with Giemsa s stain before fixing the drop The stain hemolyse the red blood cells and gives a concentrated picture of the trypanosome in situ

After several months, the posterior cervical glands will be found swollen This is called *Winterbottom s sign* The gland should be aspirated and the fluid preferably not too thick nor mixed with too much blood smeared on a slide which should not be too cold The specimen is examined under reduced light and low power magnification The unstained trypanosome has a filmy semi transparent appearance In advanced stages a *lumbar puncture* may clinch the diagnosis The fluid will be found to be opaque, or cloudy, and the pressure increased, the globulin concentration is raised and the mononuclear cell count from a few to many thousand per cubic millimeter

TREATMENT

Tryparsamide is the most useful drug for this disease The dose is 0 045 mg per kilo of body weight, given intravenously The routine course is one weekly injection for fifteen weeks When there is doubt that a cure has been obtained a second course should be given using the same dosage schedule The best treatment now in use in the Belgian Congo Nyasaland and Uganda is combined *'Bayer 205* and *tryparsamide* The Bayer 205 is injected intravenously, in a dose of 1 gm between the doses of tryparsamide

American Trypanosomiasis (Chaga's Disease)

American trypanosomiasis is an infectious disease of lower animals and man caused by the *Trypanosome Cruzi* It is vectored by the bug *Triatoma megista* Tr Cruzi invades the tissues rather than the blood stream

GEOGRAPHICAL DISTRIBUTION

This disease is common in Brazil Argentina, Uruguay Peru Ecuador Venezuela Colombia Panama Costa Rica, San Salvador, Guatemala and Mexico In countries where human infections have not been established the presence of infected animals and insect vectors has been discovered These last have been found even in California Texas, Arizona and Utah

SYMPTOMS AND SIGNS

The acute disease is usually seen in young children and begins with a fever, swelling of the face and extremities which return to normal when the temperature falls There is unilateral opthalmia (swelling of the lids and conjunctiva of one eye—called *Romana s sign*) This is sudden in onset and is accompanied usually by a reddish violet discoloration of the eyelids

conjunctival hyperemia and edema There is usually preauricular submaxillary and cervical adenopathy The heart is usually enlarged and though arrythmias are not the rule extra systoles and varying degrees of heart block may occur due to the effect upon the excitability and conductivity of the heart muscle Hepatomegaly is usual Spontaneous cure occurs in some but patients usually pass over into a chronic stage the symptoms of which are due to the multiplication of the parasites in the viscera It is believed by some that American trypanosomiasis is responsible for the chronic heart disease found in Brazil and Argentina which is the cause of many sudden deaths

DIAGNOSIS

In the acute stage the organisms can be found by direct microscopic examination of the blood or by inoculation of infected blood inso susceptible animals In the later stages after the febrile stages are over the diagnosis can only be made by the *complement fixation* reaction The antigen is a glycerin extract of the heart and spleen of infected animals

TREATMENT

There is no specific treatment Arsenical and antimony compounds are useless From recent accounts Bayer 7602 is effective The dosage is from 5 to 20 c c of a 3 per cent solution given intramuscularly

Leishmaniasis

The term leishmaniasis refers to a group of three diseases of varied appearances caused by protozoan parasites belonging to the Flagellata of the genus Leishmania

I KALA AZAR (VISCERAL LEISHMANIASIS)

Kala azar is an acute or chronic infectious disease caused by the *Leishmania donovani* It is characterized by a prolonged irregular fever splenomegaly great emaciation anemia and leucopenia The mortality is about 90 per cent in untreated cases

Geographical Distribution

The disease is widespread and occurs in Mediterranean countries South Russia India China Manchuria Abyssinia Sudan Northern and Eastern Brazil Chaco region of Argentina Paraguay Brazil border (Matto Grosso and Northern Bolivia Yungas)

Transmission

The available evidence suggests that the disease is transferred by the bites of infected sand flies of the genus Phlebotomus or other biting flies including the genus Stomoxys and possibly through the ingestion of food and drink contaminated with *Leishmania donovani* or by contact Dogs and other animals are susceptible to infection

Symptoms and Clinical Features

The onset is sudden or gradual and accompanied by rigors vomiting and high fever which may be remittent with a double crisis The fever sometimes resembles undulant fever and daily rigors are not uncommon Inguinal and cervical adenopathy hepatomegaly and splenomegaly are common There is great emaciation of the extremities and as a rule anemia is marked A dusky pigmentation is seen over the hands and feet and there may be purpura and bleeding from the gums The fever is characteristic and may be irregularly undulating with a double peak in each 24 hours Leucopenia and dysentery are common

Diagnosis

The diagnosis depends upon the demonstration of the *L donovani* either in smears or cultures of the peripheral blood glandular fluid and in the pulp of the liver and spleen Sternal and lymph gland puncture are reliable and safe Inoculation of hamsters may be of assistance Tests demonstrating the great increase in serum globulin occurring in this disease are positive in over 90 per cent of cases

Treatment

Many drugs are recommended in the recent literature for the treatment of leishmaniasis which suggests that none are entirely satisfactory *Stibamine glucoside* (neostam) has been mentioned as being useful A 2 per cent freshly prepared solution is administered intravenously on alternate days The initial

dose is 2 5 c c (0 05 gm), each succeeding dose is increased by 2 5 c c up to the maximum dose of 10 c c, the treatment is continued until from 12 to 15 doses have been given Some workers have reported only temporary benefit from this drug as well as *potassium antimony tartrate* U S P The dose of potassium antimony tartrate is 2 0 c c of a freshly prepared solution, given intravenously on alternate days each dose being increased by 1 0 c c up to the maximum dose of 5 0 c c A total of 40 doses are given but they should be reduced if toxic symptoms develop The toxic symptoms are nausea vomiting, dizziness, and collapse Coughing after administration should cause no concern

In India it has been observed that the pentavalent antimony compounds cure approximately 95 per cent of cases In those instances where antimony resistant patients are found, two new drugs have been advocated, *diamidinostilbene* and *diamidino-diphenoxy pentane* It has been reported that diamidinostilbene cures about 98 per cent of those with Indian kala azar but severe toxic reactions are noted in the form of paresthesia and partial anesthesia of the trigeminal area which does not make its appearance until several months after the administration of the drug It appears that toxic degeneration in the principal sensory nucleus of the trigeminal nerve in the pons is due to the ethylene component of the compound A less toxic drug and nearly as effective is diamidino diphenoxy pentane It is given intravenously in a 1 per cent solution in distilled water 0 025 gm as the initial dose 0 05 gm for the 2nd dose 0 075 gm for the 3rd dose then daily increases of approximately 15–20 mg until the dose reached is 1 mg per pound body weight This dose is then continued for the remainder of the course There are but few reactions to the drug Cobra venom 1 100 000 injections are advised for the paresthesia following diamidinostilbene therapy

The diet should contain whatever food the patient can tolerate It should be supplemented with vitamin B complex and if it contains less than six ounces of citrus fruit juice ascorbic acid should be given in doses of 50 mg per day

II OLD WORLD CUTANEOUS LEISHMANIASIS (ORIENTAL SORE)

This disease is sometimes called Tropical Sore, Delhi boil, Aleppo boil and cutaneous leishmaniasis The etiologic agent is the *L tropica*

Geographic Distribution

Oriental Sore may occur in countries where kala azar is endemic, but it has a distinctive distribution In Persia and Iraq it is very common while kala azar is absent Oriental sore occurs in West India but kala azar is confined to the East coast Both occur together in Central Asia One disease does not protect against the other Almost everyone in Baghdad has scars of the sores on his face The chief areas of distribution are Mediterranean countries Central Asia, Abyssinia, Sudan, Nigeria French Congo, Peru Bolivia, Brazil, the Guianas Mexico, Australia, Hunan Province, Persia, Crete and Cyprus

Transmission

Sand flies of the genus *Phlebotomus* are suspected of being vectors Since the disease can be transferred by inoculation, the possibility of contact infection must also be considered

Clinical Characteristics

The disease is characterized by small initial papules which may appear on the face arms, and legs They become covered with a dry crust from which serum exudes, and later ulcerate to form secondary sores on the margins which upon coalescing produce large raw ragged areas There may be scores of sores on the body particularly on the face and hands The ulcers have clear cut edges and indurated margins Healing occurs in from two to twelve months and leaves a depressed scar which may lead to deformity

Specific Diagnosis

The diagnosis depends upon the demonstration of *L tropica* in stained films or cultures of material aspirated from the indurated zone surrounding the ulcer It must be distinguished from the yeast cells frequently seen in the ulcerations

Treatment

If the lesions are not numerous inject into the edges of the sores 2 c c of a 1 per cent solution of *berberine sulfate* Only from one to three such treatments may be required If the lesions are numerous the treatment outlined for kala azar may be followed The injections are painful Indolent sores may require scraping and excision or plastic operations It is difficult to evaluate any treatment as the sores frequently heal spontaneously Salves and ointments are of no use Grenz rays are beneficial in many cases

III AMERICAN MUCOCUTANEOUS LEISHMANIASIS (ESPUNDIA)

This is an infectious disease caused by *L braziliensis* probably transmitted by flies of the genus *Phlebotomus* and characterized by ulcerative skin lesions and destructive ulcerations of the mouth nose and pharynx The disease is said to be common in forest regions among the collectors of chicle gum and rubber

Geographical Distribution

Mexico Central America South America including Argentina, Bolivia Brazil Colombia, Ecuador The Guianas Peru, Paraguay and Venezuela



(From Howard Fox Archives of Dermatology and Syphilology in Bercovitz Clinical Tropical Medicine Paul B Hoeber Inc)

Fig 160 American leishmaniasis in a Negro 15 years old showing a large indolent ulcer of 5 years duration on the left leg and a scar from a healed ulcer on the right leg The nasal mucosa was also affected

Clinical Characteristics

Nodular masses form in the oral and nasal mucous membranes where they set up an intractable ulceration with secondary erosion and obstruction The lymphatics are involved and death may occur from secondary complications Large portions of the nose and mouth may be destroyed

Specific Diagnosis

Yaws, leprosy and syphilis must be excluded The specific diagnosis depends upon the demonstration of *L brasiliense* in cultures or smears of material obtained by puncture of the edge of the initial ulcer or in material from nodule or ulcerations in the mucous membranes

Treatment

The treatment of the initial lesion is the same as that outlined for oriental sore *Pentavalent antimony* is advised for generalized sores *Fuadin* is used being given intramuscularly in doses of from 0 5 to 5 0 c c for 20 to 30 injections Recently *atabrine hydrochloride* has been advocated It is injected into the base of the sores 5 c c of a 10 per cent solution together with 0 1 gm tablet three times daily for seven days The treatment recommended for kala azar is used during the stage of mucous membrane involvement



(*From Howard Fox Archives of Dermatology and Syphilology in Bercovitz Clinical Tropical Medicine Paul B Hoeber Inc*)

FIG 161 American leishmaniasis of 18 months duration There was involvement of the nose lip pharynx and palate The lesion was practically healed following treatment

Spirochetal Diseases

RELAPSING FEVER

Relapsing fever is a febrile spirochetal arthropod borne infection widely distributed in many parts of the world It occurs in epidemics and is characterized by a febrile period of from four to ten days beginning and ending abruptly and followed after a week or two by a similar but milder paroxysm It exists in two principal forms—the louse borne infection of Europe and Asia and the tick borne infection of America and Africa In Africa it ranks next to malaria and sleeping sickness in prevalence

The *etiologic agent* in all cases are spirochetes

of the genus *Treponema* (*Borrelia*) though with the custom of certain authors assigning specific titles to various local strains some confusion exists in the nomenclature The louse borne organism has been called *Borrelia recurrentis* and *spirillum obermeieri* The tick borne organism has been called *Borrelia duttoni* *Borrelia novyi* and *Borrelia venezuelensis*

Louse borne relapsing fever is current in Central and Eastern Europe North Africa India Malaya China Siberia Japan and Mexico *Tick borne relapsing fever* is current in Africa Asia Europe North America Central America, Colombia and Venezuela

The *louse borne type* is transmitted from man to man by Pediculus humanus and possibly the crab louse The *tick borne type* is transmitted from animal hosts to man by soft ticks of the genus Ornithodorus These reservoir hosts include many kinds of rodents monkeys possibly bats and other mammals The ticks breed in native huts in cabins and cottages in the recreational areas of the Western United States in caves in the Colorado River Valley and in the burrows and nests of wild rodents They invade human habitations and have the feeding habits of bedbugs Attachment to the host is usually only for from 12 to 15 minutes On the American continent only endemic foci are found Epidemics in Europe and Africa depend upon overcrowding and heavy infestation with ticks and lice

Clinical Features

The incubation period is from 3 to 12 days the average being 7 days The onset is abrupt and is accompanied by headache body pains dizziness and an abrupt rise in temperature to 104 or 105 F It remains high for from a few days to a week except for slight morning remissions There may be delirium and vomiting is common Jaundice is reported in from 18 to 30 per cent of cases and splenomegaly in from 30 to 70 per cent There is usually a leucocytosis of the polymorphonuclear variety reaching 20 000 After from four to seven days the fever falls usually by crisis The patient feels more comfortable during the afebrile periods but there may be from one to eight relapses in which the same symptoms are repeated Hemorrhages frequently occur and abortion usually results in pregnant women Meningitis with recovery of the spirochete in the spinal fluid has been reported by Hawkins in Tanganyika (1941) Stupor tympanites and hiccough are frequently seen Convalescence may be protracted with nephritis conjunctivitis polyarthritis iritis parotitis pneumonia and neuritis supervening

Diagnosis

The diagnosis is made on the character of the fever leucocytosis icterus splenomegaly and presence of spirochetes in the blood or the cerebrospinal fluid or by the inoculation of the blood into white mice or rats In 20 per cent of cases the Wassermann reaction will be positive

Differential Diagnosis

The following must be considered and excluded

1 *Malaria* The finding of the parasite in the blood confirms the diagnosis
2 *Dengue Fever* In dengue there is a leucopenia and not a leucocytosis
3 *Trench Fever* Blood examination is negative for spirochetes
4 *Hemorrhagic Jaundice* Inoculation of guinea pigs produces a fatal leptospiral infection
5 *Typhus Fever* The rash appears from the fourth to the sixth day and the Weil Felix reaction or the complement deflection may determine the nature of the infection
6 *Yellow Fever* The temperature does not relapse in yellow fever The yellow fever virus may be demonstrated following the intracerebral injection of blood into mice during the first few days of the disease

Treatment

Mapharsen 0 06 gm intravenously is the most recent Army treatment One dose usually cures but 2 or 3 doses may be necessary It is most effective at the beginning of an attack or in a relapse It is dangerous at a time of crisis or just following it as the patient may collapse as a result of a Herxheimer effect Neoarsphenamine has been reported to be useless in several cases reported

from Tobruk A hypodermic injection of adrenalin may be useful every four hours in *cases of collapse* *Heilman and Herrell* have reported encouraging results with penicillin in mice infected with *B novyi*

Prevention

Measures should be taken to prevent the spread of lice from infected to normal persons To prevent tick borne disease the following measures are advised

a Avoid the occupation of native huts, cabins or houses in endemic areas

b Avoid entrance into caves inhabited by rodents bats or ticks

c Avoid soiling the hands with rodent blood in endemic areas

d Sleeping quarters should be constructed to discourage the entrance or nesting of rodents beneath floors or in the walls

e Cleanliness of barracks tents and beds *should be maintained*

f If relapsing fever occurs and is apparently the result of a tick bite a careful search should be made for ticks and after *a thorough cleaning the walls, floors* beds mattresses and other furniture should be sprayed with liquid insecticide The bedding should be sterilized by heat *Day and night clothing* and bedding should be examined after possible exposure

RAT BITE FEVER (SODOKU)

Rat bite fever is an acute febrile disease the etiologic agent being the *Spirillum minus* and the source of infection usually the bite of a wild rat and rarely of a cat weasel ferret dog or bandicoot During the bite some of the animal s blood escapes from the diseased or injured buccal mucosa into the wound or the conjunctival secretion of the rat may contaminate the wound Blood from an animal in the laboratory may infect man

Clinical Features

After an incubation period of from 1 to 60 days a primary edematous lesion with necrosis lymphangitis or lymphadenitis of the regional nodes occurs Sharp febrile paroxysms alternate with afebrile intervals and are accompanied by a rash of broad maculo papules The rash is usually purple in color, it may be urticarial or nodular, and is usually found on *the chest and arms* Myalgia and ostalgia are prominent The fatality may reach 10 per cent in untreated cases In severe cases there may be delirium and coma

Distribution

The distribution is world wide Surveys in Japan (Tokyo) Calcutta and Bombay have shown over 10 per cent of rats infected In the United States less than 100 cases were reported up until 1940 There have been cases reported in Italy Germany, England, East Africa and Australia

Diagnosis

The diagnosis is established by a history of a bite, by the demonstration of the causative organisms in darkfield preparations of the blood of white mice, white rats, and guinea *pigs inoculated with the patient's blood,* material from the primary lesion, lymph nodes or the skin macules Caution should be exercised lest the experimental mouse or rat be already *naturally infected The serum agglutinates* spirillum in low dilutions There is usually a positive Wassermann reaction

Treatment

Neosalvarsan is said to be specific but penicillin is now the drug of choice

Prevention—General Measures

Rat surveys and general eradication of rats Avoidance of rat bites, especially by not sleeping on or near earthen floors or in rat ridden communities and houses

SEVEN DAY FEVER (JAPANESE AUTUMN FEVER)

This disease is prevalent in Japan, India and the Dutch East Indies It is a febrile illness, of short duration and resembles infectious jaundice The etiologic agent is *Leptospira hebdomadis* It is found in the blood and urine in small numbers *The disease is conveyed* by the bite of small field voles The on of the disease is accompanied by fever myalgia conjunctivitis lymphadenitis, albuminuria and a slight *leucocytosis There is* no icterus

It is a mild disease the fever lasts about one

week The *diagnosis* is confirmed by serological tests and the demonstration of the leptospirae in the urine The *treatment* is symptomatic

WEIL'S DISEASE (ICTEROHEMORRHAGIC FEVER LEPTOSPIRAL JAUNDICE SPIROCHAETOSIS ICTEROHAEMORRHAGICA)

See page 149

YAWS—FRAMBESIA TROPICA

Yaws is a disease closely resembling syphilis but is confined to tropical countries This disease should not concern our armed forces greatly, since it is primarily due to a lack of personal hygiene and is not usually acquired through insect vectors The etiologic agent is the *Treponema pertenue* It is highly contagious through a breach in the skin and it is thought that the infection may be transmitted by regurgitation of infected flies when they alight on an abraded surface

The *geographic distribution* embraces tropical countries especially Africa Polynesia, the Philippines and some parts of the Western hemisphere It is prevalent in Jamaica, Haiti Trinidad Antigua and other islands of the Leeward group and in the coastal valley settlements of Colombia At present in West Africa it is epidemic and endemic

Transmission is by direct contact with lesions of infected patients and by non biting flies

Clinical Features

After an incubation period of from 3 to 4 weeks a papule appears at the site of inoculation on an abraded area It may be found on the buttock knee leg arm breast lip or inner canthus It may be either single or multiple This initial lesion is called the mother yaw There may be an accompanying fever ostalgia lymphadenitis and malaise The Wassermann reaction is usually positive in 3 to 4 weeks after the appearance of the mother yaw In from 2 to 6 weeks generalized or *secondary* lesions appear They resemble raspberries (frambesiform) or large warts but smaller papules or scaly ring worm like lesion may appear They may later disappear or they may coalesce often and form amber colored crusts In some cases this eruption shows a tendency to localize about the mouth or the anogenital region *It never appears on the mucous surfaces* Spirochetes can be recovered from the secondary lesions This eruption may last as long as two years and disappear without leaving any trace, or, it may leave pigmented spots or lichenoid eruptions like those seen in syphilis The later or tertiary stage of yaws is clinically indistinguishable from syphilis The ulcers may coalesce and the serum recovered from them give a positive Wassermann reaction In yaws the later stage frequently follows soon after the secondary lesions or in some cases even before their complete disappearance Characteristic tertiary lesions are destructive ulceration of the palate and nose (gangosa) hyperostosis of the nasal bones hard palate and the superior maxilla with obstruction of vision painful periosteal nodes on the radius ulna and tibia synovitis and tenosynovitis are frequent sabre shaped deformity of the long bones with an occasional spontaneous fracture gummas of the skin and mucous membranes disabling lesions with hyperkeratoses fissuring and ulceration of the plantar epithelium

Yaws is neither hereditary nor congenital No age or sex is exempt though males are affected more than females The disease is acquired most frequently before the age of puberty Pregnant women in the florid stage of secondary yaws have given birth to infants who remained free of the disease There is a complete absence of iritis or iridocyclitis and alopecia The macular eruption so common in syphilis is absent in yaws The central nervous and the cardiovascular systems are rarely involved Abnormalities in the spinal fluid, tabes and paresis are considered non existent or extremely rare by some others insist that there is just as much central nervous system involvement, tabes and paresis in yaws as in syphilis but that the cases are not known or brought to light as there are no institutions for them

Diagnosis

The initial and secondary lesions usually contain Treponema pertenue identified by darkfield examination The blood Wassermann and Kahn tests usually become positive in from one to two weeks after the appearance

of the initial lesion The organisms have also been found in the lymph nodes spleen and bone marrow There are some differences in the bones of syphilis and yaws the bones of yaws showing a high incidence of osteoporosis Pearce and Brown have shown that a differential diagnosis between syphilis and yaws is possible by intratesticular inoculation of rabbits In syphilis a hard lump develops and the disease spreads to the lymphatics, bones



FIG 162A
(*From Bercovitz Clinical Tropical Medicine Paul B Hoeber Inc*)

FIG 162 Yaws—Frambesia Tropica A Initial lesion on a favorite site in a child three years of age B Profuse eruption of frambesiform type The right eye is normal except for involvement of the skin of the lid C Frambesiform eruption on a favorite site

and viscera Yaws produces a granular orchitis alone Serological reactions are of little or no value in the differential diagnosis

Treatment

Yaws responds to the same therapy commonly prescribed for syphilis but favorable results are attained with much less treatment than is generally required in syphilis The preferred arsenical is *mapharsen* the adult dose of which is 0 06 gm for males and 0 04 gm for females Neoarsphenamine is also effective The dosage is 0 75 gm for adult males and 0 6 gm for adult females The preferred bismuth preparation is *bismuth subsalicylate* in oil, the dose 0 2 gm The dose for children should be governed by age and weight

The standard course of treatment recommended for yaws is four weekly injections of mapharsen or neoarsphenamine, with bismuth injections being given the same day This is to be followed without a rest period by four weekly injections of mapharsen or neoarsphenamine alone which in turn is then followed by 8 weekly injections of bismuth subsalicylate alone The patient should be followed by serologic testing at the eighth and sixteenth treatments and thereafter at three month intervals for one year If a clinical relapse occurs or if the serological test remains positive for six months after treatment has been started



Fig 162B



Fig 162C

the course as outlined before should be repeated

Penicillin effects rapid clinical cures but so far has not resulted in reversal of the positive serology in all cases

Prevention

If troops are stationed in proximity to heavily infected native populations, special care should be given to prevent the contamination of open sores and wounds by infected material

PINTA (MAL DEL PINTO—COLOMBIA CARATE)

Pinta is an infectious disease, having no relation to fungi, and caused by a spirochete which is morphologically identical with those causing syphilis and yaws Various fungi have been suspected as the etiologic agent, but since 1938 the spirochete Treponema *carateum has been accepted as the causative* agent It may be found in the tissue juice from skin lesions and lymph nodes

The *geographic distribution* of the disease is localized to damp, low lying countries particular Mexico, the West Indies and Central and South America The disease affects the dark races chiefly *It is rare in whites and is seen* most frequently in young adults from 15 to 25 years of age There is no proof of hereditary transmission and it is apparently not transmitted by contact of patient with patient There is no known vector of pinta It is not a serious disease except for the disfiguring cosmetic effect

Diagnosis

This disease is characterized by peculiar depigmented patches the eruption is symmetrical it is frequently diagnoses as syphilis The distribution of the skin lesions are localized at the outset, but later they may become generalized In rare cases the eruption may be unilateral The location is usually on the face and extremities Other sites include bony prominences such as the forehead nose, malar region knuckles and malleoli It may affect any part of the skin except the scalp The palms genitals and soles are rarely affected Small patches may be present on the mucous membranes The color of the skin is a leaden or slaty blue it may be diffuse or stippled When the blue pigmentation eventually disappears, partial depigmentation is left which may go on to complete depigmentation simulating vitiligo The course of the disease is extremely chronic The diagnosis is confirmed by biopsy of the *skin and demonstration of the spirochetes by* scrapings and darkfield examination

Treatment

The treatment is similar to that outlined for yaws

Nematode or Round Worm Infections

ANCYLOSTOMIASIS—HOOKWORM DISEASE

Etiologic Agent

In the Western hemisphere *Necator americanus* is almost exclusively the hookworm of man *Ankylostoma duodenale* and *Necator* are both prevalent in the Eastern hemisphere The dog hookworms *A braziliense* and *A caninum*, infect the skin of man in their larval stage causing the disease known as "creeping eruption" This infection is acquired usually by lying on sandy soil, beaches, etc, which have contaminated by dog excreta

Geographic Distribution

In the United States hookworm infestation occurs in the South from Virginia and Kentucky to Eastern Texas The rural population of some counties in the southern part of South Carolina Georgia, Alabama and Mississippi and in Northern Florida still show an incidence of 50 per cent or over Hookworm is prevalent in the tropics wherever the climate is moist The disease is still a serious problem in some parts of the continental United States and Puerto Rico

Transmission

The disease is transmitted by water soil, or contaminated objects harboring the infective larvae however the chief mode of infection is through the skin usually of the foot The organisms pass by way of the lymphatics to the inferior vena cava and the right heart thence in the blood stream to the lungs where they pierce the capillary walls and enter the alveoli They are then carried up the bronchi and trachea to the throat and are swallowed

They finally reach the small intestine, where they develop to maturity Eggs are hatched in the soil after being passed in the feces Eggs are found in the stools in about 4 to 6 weeks after the larvae penetrate the skin and ished adults, fifty or more worms are likely to produce clinical symptoms which are lassitude, fatigue weakness pallor, secondary anemia slight or moderate eosinophilia and edema If the stool is fresh the ova are



Fig 163A

(From Bercovitz Clinical Tropical Medicine Paul B Hoeber Inc)

Fig 163 A Pinta Extensive eruption involving the face neck trunk in a man of mixed Indian and Negro blood The face showed diffuse bluish black pigmentation Other areas of depigmentation intermingled with numerous small areas of bluish pigmentation on normal skin produced an unusual mottled appearance B Pinta Extensive depigmentation of 25 years duration in an Indian woman in Mexico City There were a few blue areas on the face

develop the next generation of larvae 5 to 8 days after being deposited on soil under favorable conditions

Specific Diagnosis

The diagnosis is made by identifying the worms or the ova in the feces In well nourished found in the four nuclear stage The ova start to develop as soon as they are excreted and in a warm moist environment, larval forms are present after 48 hours In all cases of unexplained eosinophilia a thorough stool examination should be made with con

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3 Diet—the diet should be rich in iron and supplemented with vitamins

4 An examination of the stools should be made one week after the treatment If eggs are found the treatment should be repeated until a cure is obtained

5 *Treatment of Creeping Eruption* One of the following methods should be used Repeated applications may be necessary to obtain a cure

a Saturate cotton with *ethyl acetate* apply to the area just beyond the ad vancing edge of the skin lesion and cover with adhesive tape for 24 hours

b Freeze with ethyl chloride spray or dry ice for one minute an area one inch in width just beyond the ad vancing edge of the skin lesion

Control Measures

Education as to dangers of soil pollution and methods of prevention The prevention of soil pollution by the installation of sanitary disposal systems for human discharges, es pecially sanitary privies in rural areas and the education of the public in the use of such facilities as well as in the need of wearing shoes

ASCARIASIS

This infection is caused by the *Ascaris lumbricoides*, a large intestinal worm of man The *source of infection* is the excreta of infected persons particularly children and articles soiled with such excreta in and about houses lacking sanitary facilities *Transmission* is direct or indirect the fertilized eggs from soil or other polluted material being conveyed to the mouth The eggs hatch in the intestinal canal penetrate the wall and reach the lungs by the circulatory system Most of those which reach the lungs in the blood stream reach the air passages throat and stomach and thence into the small intestine Pollu tion of soil may be carried by shoes into houses and conveyances and thus carried for long distances The worms reach maturity in the body about 2 months after infection Com municability is possible as long as mature female worms live in the intestine The pro duction of about 200 000 eggs a day permits a wide spread of fecal pollution even when the infection is light

Symptoms—Signs and Diagnosis

A few of these worms may cause no symp toms outside of restlessness gnashing of the teeth during sleep insomnia or twitching Hemoptysis may occur when the larvae are passing through the lungs, at which time they may be demonstrable in the sputum When a large infection is suspected as a cause of diarrhea, intestinal obstruction etc barium mixture by mouth with roentgen ex amination at proper intervals occasionally produces interesting findings since shadows appear which are negative at first but become positive after the worms have ingested some of the barium and the remainder has been ex pelled from the intestine The fertilized ova are usually recognized without difficulty, un fertilized ova often assume such bizarre shapes that they are frequently overlooked

Treatment

At 6 A M the patient is given five 0 2 gm *hexylresorcinol* hard gelatin capsules on an empty stomach They should be swallowed and not chewed No food is allowed for 5 hours One and one half ounces of magnesium sulfate solution are given on the following morning before breakfast If hexylresorcinol is not available *ascaridol* can be given in a dosage of 1 c c (adults) on an empty stomach followed in one hour by a saline purge

OXYURIASIS

Pinworm or oxyuriasis infection is not com monly encountered in adult patients being more common in children The etiologic agent is a small round worm *Enterobius (Oxyuris) vermicularis* The female worms migrate from the ileum to the colon and anus this occurs as a rule at night They may enter the vagina Transmission is usually by ingesting contami nated food or water Rectal itching and irritation are the chief symptoms When the infection is suspected one should not con sider a negative finding upon examination of the stool sufficient to exclude the condition Scrapings of the nail beds and perianal skin should be carefully examined for ova and, if such examinations are fruitless the final de cision should rest on whether or not the pin worms are demonstrable in the feces after a vermifuge The anal swab as specified by the

centration methods if the direct examination is negative

Treatment

The night before treatment the patient should be given a light meal, preferably free from fat No pre treatment purge is necessary unless constipation exists The drug is given in the morning on an empty stomach



Fig 163B

Food should be withheld for two hours after the treatment and alcohol for 24 hours before and after treatment A saline purge should be given on the following day if the bowels have not moved since treatment

1 *Specific Drugs*

a *In the absence of Ascaris infestation* Tetrachlorethylene The adult dose is 3 c c in a hard gelatin capsule or in 2 ounces of skimmed milk Fatal toxicity has never been reported but dizziness and drowsiness have occurred

b *In the presence of Ascaris infestation* Hexylresorcinol crystoids (Sharpe and Dohme) The adult dose is 1 0 gm All food should be avoided for four hours after treatment No toxic symptoms have been reported This will usually remove all ascaris worms and about 50 per cent of hookworms It should be followed after three days by treatment with *tetrachlorethylene* to remove the remainder of the hookworms

2 Iron therapy is indicated in all cases of hookworm showing any degree of anemia A good preparation is desiccated *ferrous* sulfate in capsules, adult dose is 0 3 gm (5 grains) three times daily after meals

but the amount of this erythema zone is not so important from the standpoint of diagnosis as are the size of the wheal and the presence of pseudopodia

If an additional diagnostic check is desired a sample of the patient s blood serum can be forwarded to the Division of Zoology of the National Institute of Health Washington D C for a precipitin test The following *precautions should be observed in securing the* sample (1) Serum for the test should be secured either before or at least 24 hours after the application of the intradermal test (2) The patient should be bled before breakfast in order to avoid chylous specimens and prevent deterioration of the sample enroute (3) All apparatus used for collection should be washed free from alkali and acid before sterilization (4) Only sterile apparatus should be used (5) The syringe used in drawing the blood should be rinsed with physiological saline solution to prevent hemolysis (6) The serum should be separated from the clot before hemolysis begins and rendered free from red cells and particles by centrifuging (7) At least 2 cc of perfectly clear serum should be submitted about 5 c c of blood will provide this (8) Do not heat or add preservative of any nature

Treatment

Free saline purgation if given early may eliminate some of the worms Drug therapy is very disappointing and not of much value The mortality is 5 to 15 per cent

TRICHURIASIS

This infection is caused by *Trichuris trichiura* commonly called the whipworm The worms invade the large intestine and are not infrequently found in the appendix The ova are found in the stools and are recognized by their characteristic oval shape with a button like projection at either end Diarrhea anemia urticaria and eosinophilia may occur The treatment is the same as that recommended for ascariasis *Leche de Higueron* is said to be efficacious but is unobtainable in the United States

STRONGYLOIDOSIS

Strongyloides stercoralis infection is endemic wherever hookworm disease exists The worms may cause diarrhea by invading the upper small intestine The life cycle and invasion method are very similar to those of the hookworm Many people harbor the worms without developing symptoms The diagnosis is made by finding the larvae in the stools They may be confused with meat fiber but being actively motile are distinguishable

Treatment

Gentian Violet Enseals grain 1, three times daily for 16 days before meals is the best treatment Treatment should be stopped if there is severe epigastric pain pronounced and persistent nausea or a violet discoloration of the urine

FILARIASIS

Filariasis is an infectious disease caused by the invasion of the lymphatics by various species of filaria a nematode worm The term usually refers to infection with *Wuchereria bancrofti* because of its world wide distribution It is found in almost all warm countries it has been reported as far north as Washington, D C, and as far south as the Argentine It is common from Shantung Province in China and Southern Japan to a large portion of Northern Australia Arabia Madagascar and most of Africa are endemic areas of infection

Symptoms and Signs

The disease is characterized by recurrent lymphadenitis particularly of the lower extremities, accompanied by febrile phenomena chyluria and later evidence of lymphatic obstruction of the lower portion of the body such as elephantiasis varicose lymph glands and lymph scrotum Before the development of symptoms embryos are found in the night blood embryos are generally not found in the circulating blood after the development of marked symptoms

Transmission

The adult worms live in the lymphatic system of infected persons and release larvae (microfilariae) into the lymph and blood stream Some thirty two varieties of night biting mosquitoes serve as intermediate hosts The most common transmitters are *Culex fatigans Culex pipiens Aedes variegatus*

National Institute of Health is of diagnostic value

Treatment

Two ½ grain enteric coated or "Enseals" tablets of *gentian violet* should be given three times daily before meals for 8 days After a rest period of one week, the course can be repeated Nausea frequently follows the use of the drug and it may have to be discontinued *Tetrachlorethylene* is an effective one dose treatment for light infestations It is given orally at the rate of 0 1 c c for each year of age in a suitable dose of magnesium citrate

TRICHINOSIS

Trichinosis sometimes called trichiniasis is a disease caused by the *Trichinella spiralis*, transmitted only through the consumption of meat containing viable infective larvae The meat is usually uncooked or insufficiently cooked pork and less frequently the meat of other animals The onset usually occurs in from 6 to 7 days after ingestion of the infected meat In heavy infestations, gastro intestinal symptoms may appear in 24 hours The prevalence of this condition is world wide The parasite is particularly widespread in the United States about one in every six necropsies showing infection The disease is frequently confused with other illnesses After ingestion of the infected meat the cysts are digested and the larvae liberated when they mature sexually and copulate The males die and are expelled in the feces The females burrow into the intestinal mucosa and since reproduction is viviparous the larvae are discharged into the veins and lymphatics, and at the beginning of the second week, migrate to the muscles, by way of the arterial blood It is during this period that the physician is usually first consulted

Signs and Symptoms

Nausea vomiting or diarrhea may be present Muscle soreness or pain edema of the face or eyelids laryngitis subcutaneous hemorrhages, cough pain in the chest difficulty in swallowing, and labored breathing may occur even pneumonia or involvement of the central nervous system in some cases An intermittent fever is usual Eosinophilia is usually marked It may occasionally be absent in overwhelming infections and in individuals suffering from bacterial or virus infections The symptoms are extremely variable Intradermal and precipitin tests should be employed as diagnostic aids Direct microscopic examination of a biopsied sample of deltoid or gastrocnemius muscle, pressed or digested in artificial gastric juice may detect larvae after the 21st day of infection The first examination which might yield a positive diagnosis is the search for the migrating larvae in the arterial blood This is done by taking from 5 to 10 c c of arterial blood and laking it with 10 to 15 volumes of 3 per cent acetic acid, centrifuging washing the sediment, centrifuging again and examining the sediment under the microscope The migratory larvae measure 100 by 6 microns and are granular in appearance except for a refractile anterior cap At this stage of the infection, the skin test should give positive, or at least a delayed positive reaction The precipitin test should be at least weakly positive and increase in titre during convalescence

Technique of the Skin Test

The forearm of the patient is the preferred site for the test It is scrubbed with alcohol and allowed to dry Using a syringe fitted with a No 26 gauge ½ inch needle, 0 01 c c of the 1 10,000 dilution of the antigen is injected intradermally Since the antigen is prepared with physiologic saline solution this solution may be used alone as a control

A positive reaction to the intradermal test is of the immediate type and appears usually within 15 to 20 minutes after the injection of the antigen In rare cases there may be a *delayed reaction which does not reach* its height before 24 hours In using the antigen it is therefore necessary to observe the patient at the end of 24 hours provided the initial reading has been negative Since no arbitrary standards can be laid down for evaluating the test, judgement must be used in interpreting the reaction It is considered that the formation of a wheal with a diameter larger than the control wheal (by 3 millimeters or more) with or without pseudopodia, represents a positive reaction to the test The wheal is usually surrounded by a zone of erythema

Mic ofla ns t ken up by an app op ate host (m qu t) b g a ca r of the d a p s t the stomach and) e the r sh th Th y then p netr t the w ll of the tom h and become e y led n the tho a c m s l s. Inserts (abo) show success e stages of de elopm t n the mo qu r

Th m qu to b tes a othe ho t The matu ed l rvae that now h e m g at d to th m qu t h d p e Dutto m mb e a d re ady to p etr t th sk n of th new host e ther th gh th p n t e wo d or other nc dental b e k and e t r the lymph t cs a blo d e sels

Th m tu ed f l s n the lymph t cs extr de mult pl yo ng (m crof l) wh ch c l t nth bl od a d are taken up aga n by m q to wh they bi t the f ct d host I se t show a m ro f la la in the blood tream

Th se fect e stag la ae m g t su lly t the p l c lymphat s wh re th y m t e a d p pag te The bl ck d lymph t c a e d ma (ele phant s) (the l gs c tum or other p t dep nd g upon wh e the ar ae h e lodg d I t hows a of the ca led a gan m a lym phat c essel

Anopheles rossi and *A costalis* A period of about 10 days is required for the development of the microfilariae during which time the worms migrate to the mouth parts of the mosquito Man is infected through the bite of an infected mosquito

Specific Diagnosis

After an indefinite period of incubation symptoms are produced by invasion of the lymphatics usually the inguinal The initial attack is characterized by lymphangitis, local signs, fever, and malaise which may persist for several days The attacks recur and chronic elephantoid manifestations tend to develop, due to blockage of the lymphatic Edema is confined mostly to the lower extremities groin and scrotum The specific diagnosis is made by identification of the microfilariae in the peripheral blood stream The nocturnal periodicity of appearance of the microfilariae in the peripheral blood stream is characteristic with increment in the evening and decrement in the early morning hours This can be reversed by a change of habit whereby the host sleeps by day and is active at night In certain Pacific islands some microfilariae show no periodicity at all It is well to take blood smears between 9 P M and midnight Fresh blood shows the parasite in motion The thin smear is useful for identifying the species

At times, aspiration of an enlarged lymph gland vessel or hydrocele may result in the discovery of the microfilariae Roentgenograms also are of assistance in a few cases after the parasite has become calcified The absence of *Wucheria* in the blood does not exclude the diagnosis because the parent worms may have died or lymphatic obstruction may be so complete that the embryos cannot gain access to the blood stream A complement fixation test has given fairly reliable results its antigen is prepared from *Dirofilaria immitis*, the dog heartworm this represents a group reaction and is not specific for the *Wucheria bancrofti* A cutaneous test using the same antigen has been tried but it has not been of much use It is more reliable for L Loa than W bancrofti infections

Treatment

There is no specific treatment The acute lymphangitis usually caused by hemolytic streptococci is treated by sulfapyridine which is recommended as the most effective drug by Earle (11) The initial dose is 2 grams with subsequent doses of 1 gram every 4 hours day and night until five days of normal temperature have elapsed The subsequent dosage may be modified after 2 days of normal temperature at the discretion of the medical officer Chyluria is treated by rest in bed with the feet elevated, the bladder is washed out with boric acid and a solution introduced Liq ad renal 1 1000 29 5 c c. zinc sulfate 0 324 gm , and boric acid 295 c c Surgical treatment is reserved for elephantiasis Large varicose glands in the groins are not removed since fistulae and elephantiasis will surely result Elephantiasis of the legs is managed by elevation and elastic bandages free incision into the fascia lata and removal of strips of aponeurosis The scrotum can be removed the testes and cord separated and hypertrophied gubernaculae divided

Prevention

This is concerned with the prevention of bites of the mosquitoes which serve as intermediary hosts Screening of residences with at least No 18 mesh screen Temporary utilization of bed nets or repellants if screening is not available Breeding places of the mosquitoes should be eliminated or sprayed with larvacides such as DDT

ONCHOCERCIASIS

This disease is produced by the *Onchocerca volvulus* a filarial parasite which produces nodules in the skin eye lesions and blindness The disease is found in Africa, the Western slope of Guatamela at altitudes of from 2 000 to 6 000 feet Southern Mexico in the states of Chiapas Caxaca Guerrero and Yucatan and in well watered areas of Central America

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(Courtesy The Seminar published by Sharp & Dohme Inc)

Fig 164 Diagram Depicting the Pathogenesis of Filarial Infection

Microfilariae taken up by an appropriate host (mosquito) in biting a carrier of the disease, pass to the stomach and lose the sheath. They then penetrate the wall of the stomach and become encysted in the thoracic muscles. [illegible] (above) show successive stages of development in the mosquito.

The mosquito bites another host. The mat red lar ae that now ha e migrated to the mosq to s h ad p D tro s m mbran and a e eady to p et te the sk of the new host eith thro gh the p tu e wou d or other inc dental b eak and e s the lymphatics a blood [illegible]

The e fect e tage for ea m g te s ally to the p l ic lymphatics wh e th y matu e a d p op gate The blocked lymphatics cau e dema (ele phanti a) of the leg scrotum o other pa ts depend ng po whe e the lar ae h e lodg d [illegible] e t shows one of th co led orga ms a lymphat c [illegible]

The m t red f lar s i the lymphat c [illegible] de m lt ple you g (m crof la ae) wh ch ci c late in the blood and ar t ken up aga n by mosq toes when they b te the fect d host Inse t shows a m c a f laria in the blood stream

Transmission

The adult worms are located principally in *subcutaneous tumors in the occipital and* temporo frontal regions releasing microfilariae into the adjacent lymphatics and other tissues The embryos are rarely found in the peripheral blood Various species of black gnats (*Simulium*) serve as intermediate hosts After infection with the embryos, obtained by biting an infected person, a minimum period of six days is required for the larval development of the worm in the insect during which time the worms migrate to the gnat's mouth Man is *infected by introduction of the parasite into* the wound made by an infected gnat

Symptoms

Peculiar subcutaneous fibroid tumors are seen ranging in size from a pea to a pigeon's egg Tumors on the scalp may measure from 6 to 30 mm in diameter They are tender, freely movable and easily enucleated They may cause epileptiform attacks due to perforation of the cranium by a tumor of the periosteum There may be lymphatic enlargement of the scrotum hydrocele and enlarged testes Elephantiasis of lesser degree than that seen with W *bancrofti* has been reported

In about 5 per cent of cases ocular complications occur due to the migration of the microfilariae into the eye producing a keratitis, iritis and conjunctivitis Photophobia xerosis and impairment of vision follow, sometimes to the extent of complete blindness They are usually associated with erysipelatoid inflammation of the face neuralgia and pyrexia Eye lesions are late manifestations

Erysipelatoid rashes of the skin are common as are also lichenoid eruptions in Europeans affected with the disease There may be a general lichenoid dermatitis with intense itching particularly at night The skin may be thickened and wrinkled and a peculiar enlargement of the pinna of the ear may result

Diagnosis

The diagnosis is made by *the identification* of adult worms removed from tumors or of microfilariae from adjacent tissues (biopsy or aspiration) A piece of skin near an onchocerca nodule is snipped off placed in saline solution for fifteen minutes at 37°C and centrifuged The bottom layer, containing microfilariae which have escaped from the tissue is then removed with a pipette

Treatment

There is practically no treatment Early enucleation of nodules and careful observation for the development of new ones are advised Puncture, aspiration with a hypodermic syringe and examination for microfilariae should be done as soon as a nodule is suspected Protective measures are the wearing of flyproof clothing and veils An insect repellant should be applied to exposed parts several times daily A smudge of smoke should be employed to keep the flies away from an encampment or out of buildings The adult gnats only bite during daylight

Cestode or Tapeworm Infections

INTESTINAL TAENIASIS

Four species of tapeworm are commonly found in man They are

1 *Pork Tapeworm or Taenia solium* This is rare in the United States but is common in Europe and Asia Man acquires the infection by eating improperly cooked pork Usually one worm is harbored at a time, but it may survive for many years its head being attached to the wall of the jejunum or the upper ileum Cysts may develop in remote parts of the body as a hydatid disease It is difficult to differentiate it from the beef tapeworm
2 *Beef Tapeworm or Taenia saginata* The beef tapeworm is common in North America It may grow to a length of 15 to 20 feet It enters the body in infected beef Examination of the segments in the feces affords the simplest and quickest method of diagnosis They are the mature and gravid proglottids

   From the structure of these segments the beef and the pork tapeworms can be differentiated The ova are of no value in the differentiation It is important to distinguish between the two since in pork tapeworm infection man may act as intermediate host as well as the definitive host The gravid segments are compressed between glass slides and the num

ber of branchings from the main body of the uterus carefully noted Those of *T solium* number between 12 and 20 those of *T saginata* number between 40 and 50 If the entire worm is available for examination the differentiation is easy because of the distinctive character of the head or scolex The scolex of *T solium* bears a double row of hooks, the head of *T saginata* bears no hooklets but four large sucking discs instead The most distal segments should be examined when the entire worm is available since only in these will the uterine branchings be visible It should be observed that these segments are much longer than they are wide This is of importance in the differentiation from the fish tapeworm or *Diphyllobothrium latum* whose mature segments are wider than they are long and have a centrally placed relatively small, coiled uterus The ova of this fish tapeworm are readily distinguished from those of the aforementioned taeniae in that they are larger contain an operculum but no striated border

3 *Fish Tapeworm or Diphyllobothrium latum* These worms were originally found mainly in Northern Europe but have been introduced into the Great Lakes and southern Canada region by Scandinavian immigrants Dogs and bears as well as man are infected Many doubt that these worms are a common cause of a macrocytic anemia The diagnostic characteristics have already been mentioned

4 *Dwarf Tapeworm or Hymenolepis nana* This is the most common tapeworm in this country being found mostly in children in the southern part of the United States It is also common in Italy The worms become attached to the jejunal mucosa Rats and mice serve as reservoirs The diagnosis is made by recognizing the ova in the stools They are round and have a thin double shell

Treatment of Tapeworm Infection

The treatment cannot be considered effective unless the entire worm including the head or scolex is removed If this is not done and the head is left the entire worm will regenerate in a few months For the beef or pork tapeworm *oleoresin of male fern* is the best treatment On the day preceding the treatment the patient is given one and one half ounces of magnesium sulfate solution at 8 P M No breakfast is given the following morning and at 8 A M of the day of treatment 6 capsules are freshly prepared each containing 10 minims of oleoresin of male fern Two capsules are given for three doses one half hour apart At noon time the patient is given one and one half ounces of *magnesium sulfate* solution The patient is told to remain in bed and no food is allowed until the bowels have moved freely The stools should be passed into water and all segments saved for examination For the dwarf tapeworm *hexylresorcinol* is used as for ascaris infection See page 825 If it fails the patient is treated as for beef and pork tapeworm *Carbon tetrachloride* is used by some, but the scolex because of its digestion by this agent may be impossible to recognize Infection with the fish tapeworm can also be treated by *oleoresin of male fern*

CYSTICERCOSIS

Accidental ingestion of the ripe ova of *T solium* may result in man becoming the intermediate host The cysticerci may migrate to the muscles of the neck and to the ribs lung tongue liver heart and eye and especially the brain Ocular involvement and nervous symptoms such as Jacksonian convulsions biting of the tongue, incontinence mental degeneration and loss of memory and the higher senses The cysticerci may die and become calcified forming painful subcutaneous nodules or intramuscular swellings They are frequently diagnosed accidentally by roentgen study if the cyst happens to be calcified There may be palpable cysts in the tissues from all sizes up to that of a hen s egg Eosinophilia gives no aid in diagnosis Complement fixation tests are inconclusive The intradermal Casoni test is positive in about 50 per cent Treatment is rarely of any value

ECHINOCOCCUS DISEASE

The larval forms *Taenia echinococcus* of Echinococcus granulosus may invade the human body The hydatid stage is sometimes found in cattle sheep and hog raisers As a rule the liver is the chief organ affected but

Transmission

The adult worms are located principally in subcutaneous tumors in the occipital and temporo frontal regions releasing microfilariae into the adjacent lymphatics and other tissues The embryos are rarely found in the peripheral blood Various species of black gnats (*Simulium*) serve as intermediate hosts After infection with the embryos, obtained by biting an infected person, a minimum period of six days is required for the larval development of the worm in the insect, during which time the worms migrate to the gnat s mouth Man is *infected by introduction of the* parasite into the wound made by an infected gnat

Symptoms

Peculiar subcutaneous fibroid tumors are seen, ranging in size from a pea to a pigeon's egg Tumors on the scalp may measure from 6 to 30 mm in diameter They are tender, freely movable and easily enucleated They may cause epileptiform attacks due to perforation of the cranium by a tumor of the periosteum There may be lymphatic enlargement of the scrotum hydrocele, and enlarged testes Elephantiasis of lesser degree than that seen with *W bancrofti* has been reported

In about 5 per cent of cases ocular complications occur due to the migration of the microfilariae into the eye producing a keratitis iritis and conjunctivitis Photophobia xerosis and impairment of vision follow sometimes to the extent of complete blindness They are usually associated with erysipelatoid inflammation of the face neuralgia and pyrexia Eye lesions are late manifestations

Erysipelatoid rashes of the skin are common, as are also lichenoid eruptions in Europeans affected with the disease There may be a general lichenoid dermatitis with intense itching particularly at night The skin may be thickened and wrinkled and a peculiar enlargement of the pinna of the ear may result

Diagnosis

The diagnosis is made by the identification of adult worms removed from tumors or of microfilariae from adjacent tissues (biopsy or aspiration) A piece of skin near an onchocerca nodule is snipped off placed in saline solution for fifteen minutes at 37°C and centrifuged The bottom layer, containing microfilariae which have escaped from the tissue is then removed with a pipette

Treatment

There is practically no treatment Early enucleation of nodules and careful observation for the development of new ones are advised Puncture, aspiration with a hypodermic syringe and examination for microfilariae should be done as soon as a nodule is suspected Protective measures are the wearing of flyproof clothing and veils An insect repellant should be applied to exposed parts several times daily A smudge of smoke should be employed to keep the flies away from an encampment or out of buildings The adult gnats only bite during daylight

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podia It reaches maximal proportions in half an hour and then disappears The wheal should be at least 2 5 cm in diameter A *delayed reaction* is manifested by the erythema and induration appearing in a few hours and lasting twenty four hours The area of edema and infiltration should be at least 4 cm in diameter

The test is considered about 95 per cent accu rate it may remain positive throughout the patient s life even after the disease has been cured Skin allergy may cause a false response to the test and it may also be activated by other helminth infections If the cyst possesses no antigenic properties, the test may be negative It has been shown that antigens prepared from other helminths are nearly as effective as that of the echinococcus itself

II *The Complement Fixation Test* This test is reliable in about 75 per cent of cases It gives positive readings as long as there is a living cyst in the body Negative readings are obtained if the cyst becomes calcified The antigen used in cyst fluid which has been fil tered and preserved with 0 5 per cent phenol A control using strongly positive syphilitic serum is carried out simultaneously

III *The Precipitin Test* Equal parts of the patient's serum and filtered hydatid cyst fluid are mixed and incubated for one hour at 37 C The presence of a flocculum is sugges tive a positive reaction but it should be noted that false positive reactions are frequent

Treatment

The treatment of this disease is the surgical removal of the cysts which are carefully opened emptied and either enucleated or marsupialized

Trematode Infections

BILHARZIASIS (SCHISTOSOMIASIS)

I Intestinal Bilhar iasis

This disease is also called schistosomiasis The etiologic agent is the *Schistosoma mansoni* a blood fluke The *geographical distribution* of the disease embraces Africa Brazil Dutch Guiana and Venezuela Panama and the Canal Zone in Central America Puerto Rico Vie ques the Lesser Antilles including St Lucia Antigua St Kitts Nevis Monsterrat Mar tinique Guadeloupe and St Martin It is usually more common in men The infection is acquired during the period of shallow water when the concentration of the cercariae is highest

Transmission The transmission of schisto somiasis from man to man or from animal to man is dependent upon the intermediary de velopment of the schistosome in a suitable variety of molluscan host Fresh water snails which are common in ponds canals rice pad dies and irrigation ditches act as intermediate hosts becoming infected from the feces of those harboring the disease Man in turn becomes infected by wading or bathing in such water So far as is known all flukes which are parasitic in man reproduce by means of fertilized eggs and by a process of internal budding which gives rise to one or more asexual generations this latter phase must take place in a molluscan host

The life cycle of the various blood flukes *S mansoni*, *S japonicum*, and *S hematobium* is identical except for the organ the adult worm selects to deposit its eggs in The eggs of *S mansoni* and *S japonicum* are laid in the mesenteric branches of the portal system where they are swept into the liver adhere to the capillary walls trapped in the tissues of nearby organs or extruded by vessels of the bowel epithelium whence they pass into the lumen of the bowel and are passed from the body with the feces The eggs of *S hematobium* are extruded from the vessels of the bladder wall and upon escaping into the urine, cause ulcera tion of the bladder

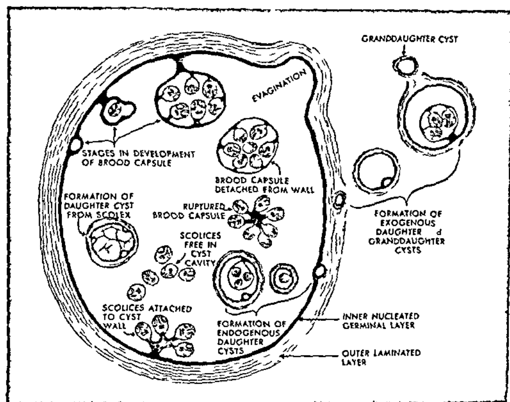
The worms live in the branches of the mesen teric or pelvic vein where they feed on the blood corpuscles From this location the female worm leaves her male partner and makes excur sions into the smallest vessels into which she force her slender body She deposits her eggs, one at a time in the vessels adjacent to the walls of the bladder or rectum The eggs in turn gradually work their way through the vessels into the walls of the bladder or intes tine and finally into the cavity of these organs whence they escape with the urine or feces The eggs are immature when they are laid but they contain fully developed miracidia by the time they escape from the body They hatch within a few hours after falling into fresh water and the emerging miracidia seek the snails which act as the intermediary hosts

the disease may also invade the lungs, kidneys, spleen heart and brain The disease has been found to prevail in Iceland, Central Europe, Argentina Australia Arabia, Tunis Algeria, Brazil, Uruguay and Africa It is uncommon in the United States

Cysts follow the deposition of the eggs in the various parts to which they come to rest The inner germinal layer of the cyst produces buds that soon develop into daughter cysts which become free in the hydatid fluid and in turn

Diagnosis

It is rarely possible to diagnose this disease on clinical grounds or findings alone One might suspect its presence if there is a history of close association with dogs in an endemic area as well as symptoms of visceral dysfunction There may be cystic swellings which give the hydatid thrill' when percussed, there may be palpable smooth rounded tumors of the liver As a rule the final diagnosis is made by operative intervention biopsy of the cyst



(*Courtesy The Seminar published by Sharp & Dohme Inc*)

FIG 165 Diagrammatic Representation Showing the Various Stages in the Development of Echinococcal Cysts

form other cysts (unilocular cysts) In this manner, over 2 000,000 new organisms may arise from a single ovum Scolices develop in the cysts and represent the heads of future worms in the event of their transfer to the intestines of dogs Daughter cysts are sometimes produced by an evagination of the cyst wall In this manner metastases may occur The cysts may grow slowly to reach large lobulated masses and may rupture if not removed surgically or they may die and undergo *fibrosis and calcification*

wall or by laboratory tests Demonstration of scolices or hooklets remain the final evidence of the disease but when echinococcic disease is suspected three laboratory procedures are suggested

I *Intradermal Test of Casoni* In this test 0 25 c c of fluid obtained aseptically from infected cattle or sheep is injected into the skin of the upper arm A saline control is run at the same time An *immediate positive* reaction is manifested by a rapidly increasing bleb with a surrounding area of erythema and pseudo

They penetrate into the snail tissues within a period of one half hour after finding the proper snail species The miracidia live for only a few hours and therefore must find a snail within this time In the soft tissues of the snail they develop into sporocysts which produce a second generation of sporocysts, which in turn produce the cercariae These forked tail cercariae burst the walls of the parent sporocyst and finally escape from the snail into the water They may continue to emerge from the snail in swarms for several weeks The cercariae must reach a host within three days or they perish They are attracted to human skin which they penetrate losing their formed tails In the case of *S japonicum* farm animals also play the role of definitive hosts which makes the eradication of this disease particularly difficult

The snails may be found in fresh water with a slight alkaline reaction usually containing aquatic vegetation and occasionally in brackish water They may inhabit slow moving streams irrigation ditches limestone sinks, reservoirs and small pools after flooding of streams Thus the disease is contracted while bathing wading working or washing clothes in infected water and possibly through the use of a polluted public water supply

Diagnosis There is an early dermatitis at the site of penetration of the cercariae About six to eight weeks after the initial infection there are fever urticaria, abdominal pain rigors eosinophilia bloody stools containing the lateral spined ova There may be pulmonary symptoms with cough and hepatic and splenic tenderness Leucocytosis may reach 30 000 with an eosinophilia of from 30 to 70 per cent Proctoscopic examination is of assistance in the diagnosis There may be choleraic diarrhea In the late or terminal stage there may be massive abdominal tumors with rectal polyps and fistulae prolapse of the rectum blood and ova in the stools splenomegaly cirrhosis of the liver with ascites pneumonia from deposition of the eggs in the lungs bilharzial appendicitis and infiltration of the buttocks with eggs

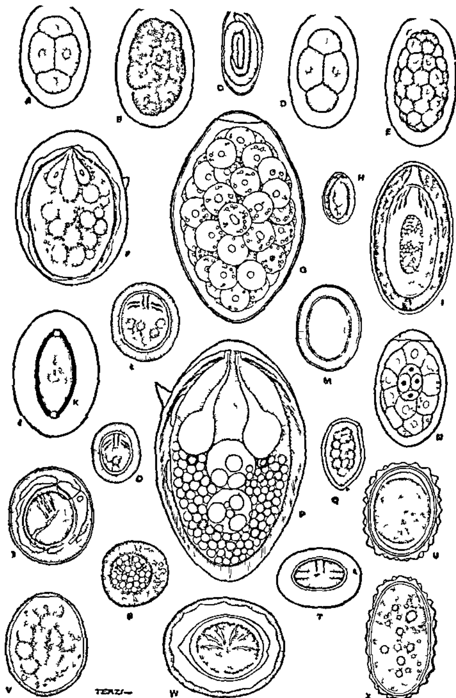
II Urinary Bilharziasis

This disease is caused by the *Schistosoma hematobium* It is a disease of great antiquity eggs being found in mummies of the First Egyptian Dynasty It is widespread now in Africa, Egypt in the Nile Valley along the Mediterranean Coast as far west as Morocco, in East Africa from the Sudan and Ethiopia to the Union of South Africa in the Congo Basin and in West Africa from Nigeria to Senegal and those countries along the Gulf of Guinea It is present in Madagascar Mauritius, Palestine Syria Arabia, Iraq Greece Cyprus and Portugal

Pathology The adult worms are found in the veins of the urinary bladder genitalia and perineum The eggs escape into the urine and cause ulceration of the bladder Urinary calculi may form about the eggs as a nuclei Secondary infection of ascending renal type is common and where the eggs are deposited in the urethral walls or the kidney pelves obstruction and nephrosis can follow Urethral fistulas vaginal polyps enlargement of the penis and labia may follow the deposition of eggs in the prostate seminal vesicles epididymus penis urethra cervix or vagina In heavy infections the eggs can be carried to the lungs in large numbers leading to pulmonary fibrosis and embarrassment of the pulmonary circulation

Symptoms Pain urgency frequency and burning on micturition are common early symptoms Blood occasionally in clots may be passed at the end of micturition Pain is by no means always a predominant feature there may be a dull oppressive feeling in the suprapubic region a deep seated ache in the perineum or a scalding sensation upon micturition Rectal symptoms such as the passage of blood and mucus may be present as well and a digital or proctoscopic examination may detect ulceration above the lobes of the prostate gland Besides the vesical symptoms there may be signs of prostatic disease or even disease of the seminal vesicles with spermatorrhea Eggs can be found in the seminal fluid Excresences about the anus groin and perineum require microscopical examination to be differentiated from venereal warts or condylomata

Diagnosis The eggs are easily found in the urine They measure about 150 by 50 micra and have a terminal spine at one end as well as a thin transparent shell They may be more easily found by centrifuging the urine or examining the last portion passed Cystos-



(From Nelsons Loose leaf Medicine Thomas Nelson and Son)

FIG 166 Eggs of various parasitic worms that may be found in the feces × about 400
(After Castellani and Chalmers Drawings collected by them from the works of various authors)

A Ancylostoma duodenale
B Nematode (? species egg of Strongyloides stercoralis according to Thayer but egg of this species as seen in the feces is only about 50μ long and contains a well formed embryo)
C Oxyuris (Enterobius) vermicularis
D Necator americanus
E Trichostrongylus colubriformus
F Schistosoma japonicum
G Fasciolopsis buski
H Heterophyes heterophyes
I Macracanthorhynchus hiradinaceus
J Diphyllobothrium cordatum
K Trichiuris trichiura (placed inside to save space)
L Taenia solium
M Taenia confusa
N Diphyllobothrium latum
O Taenia saginata
P Schistosoma mansoni
Q *Dicrocoelium dendriticum*
R Hymenolepis nana
S Dipylidium caninum (eggs usually grouped in packets)
T *Hymenolepis lanceolata*
U Ascaris lumbricoides (fertile egg)
V Diplogonoporus grandis
W Hymenolepis diminuta
X Ascaris lumbricoides (infertile egg)

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copy will reveal sparse, gray, discrete elevations around the urethral orifices, later there will be hemorrhagic areas with surrounding hyperemia, and in advanced cases, ridges like 'sea sand' will be present with papillomata

1 *Intradermal Test* This is similar to the Casoni test A saline extract of snail livers (*Pl exustus*) is infected with *B spindalis,* filtered until free of bacteria and injected intradermally The amount used is 4 minims The reaction may be immediate or delayed for from 5 to 18 hours It remains positive for years after a cure
2 *Complement Fixation Test* This is performed as for the Wassermann test using an antigen prepared from snails' livers infected with the cercariae of *B mansoni*

Differential Diagnosis One must exclude cystitis nephritis bladder or renal calculi, papilloma or carcinoma of the urinary tract tuberculosis and gonorrhea

III Eastern Bilharziasis (Asiatic Schistosomiasis)

This is a serious chronic endemic disease of the Far East caused by the *Schistosoma japonicum* *Geographical Distribution* The chief endemic area of this disease is in China and involves the Yangtze Valley from Shanghai to the Szechuan Province above Chengtu and South in Hunan Province It is present along the South China Coast as far as Canton In Southwest China it is present in Yunan Province and across the divide in the upper regions of Burma It is present in Japan Formosa the Philippines Samar Leyte, Mindanao and on the island of Celebes

Pathology The adult worms live exclusively in the mesenteric portal system In the intestine, the entire colon and often the lower portion of the small intestine is involved Scarring of the intestine leads to thickening peritoneal adhesions and to the subsequent formation of hundreds of small papillomas which protrude into the lumen of the gut Eggs are carried to the liver where they produce abscesses about the portal venules Scarring portal cirrhosis splenomegaly and ascites follow The urinary bladder is unaffected

Clinical Features In the early stage fever urticaria, pulmonary rales, abdominal discomfort, eosinophilia, dermatographia, leucocytosis and a cercarial dermatitis may be present These may be followed by marked emaciation, dysentery, and hepatomegaly and splenomegaly In the terminal stages (3 to 5 years), there are severe anemia, ascites, edema of the lower extremities, hemiplegia, blindness Jacksonian epilepsy and bloody diarrhea

Diagnosis The diagnosis rests upon finding the eggs in the feces Concentration of the feces by emulsifying them in normal saline, straining through gauze and washing in saline repeatedly and then examining the sediment *may reveal light infections In addition to* eosinophilia and leucocytosis anemia may develop Urticaria with eosinophilia is usually suggestive A biopsy of liver by puncture with a wide borne needle or operation for splenectomy usually demonstrates the eggs The *formaldehyde serum test is usually positive*

Differential Diagnosis The following must be excluded typhoid fever miliary tuberculosis amebic and bacillary dysentery, amebic abscess of the liver, and, in the later stages, the various types of hepatic cirrhosis, chronic malaria, kala azar and the various forms of splenomegaly

Treatment

Fuadin is given intramuscularly in doses of 1 5 c c 3 5 c c, and 5 0 c c on successive days then 5 0 c c on alternate days to a total of ten doses *Toxic symptoms* are vomiting and joint pains After conclusion of the treatment the feces and urine should be examined for viable eggs if they are found or the symptoms persist, repeat the course of treatment after a two weeks rest period If a satisfactory response does not result from three courses of *fuadin* one should give *potassium antimony tartrate* U S P intravenously in a 2 per cent freshly prepared solution on alternate days the initial dose is 2 5 c c (0 05 gm) each subsequent dose is increased by 1 25 c c until 7 5 c c have been taken A total of 15 to 14 doses should be given The drug should be administered after a light meal the patient should then lie down for two or three hours *Anthiomaline* is considered better than tartar emetic The total dose required is 50 c c or 0 3 gm of metallic antimony This is given *intramuscularly* in 12

injections on alternate days one of 1 5 c c one of 3 c c and ten of 4 25 c c each *Emetine hydrochloride* is suggested for those who are resistant to antimony It is given intravenously ½ grain in solution The maximum dose for children is 1 grain with a total of 15 grains The maximum dose for adults is one and one half grains daily with a total of 20 grains The drug is toxic When potassium antimony tartrate is given it should be administered slowly into the vein to avoid thrombosis It will cause necrosis if introduced into the subcutaneous tissues The toxic symptoms are nausea, vomiting dizziness and collapse Coughing may occur after administration but is no cause for concern Contraindications to antimony preparations are nephritis jaundice or severe liver disease

In the Eastern type of the disease *splenectomy* is usually of no avail owing to the presence of advanced cirrhosis of the liver In the intestinal type early splenectomy is advised The mortality is said to be 15 per cent Other operative measures advised are the excision of 12 to 15 inches of the rectal and sigmoid mucosa This is not advised in anemic or debilitated patients Associated hookworm disease should be treated vigorously

The *diet* should consist of all the essential nutrient substances If there is evidence of hepatic disease adequate dietary measures should be instituted There is no need to restrict proteins Milk eggs and cheese are permissible The diet should be supplemented with vitamin A and the B complex

The criterion of cure is a cessation of the passage of eggs containing living embryos If a cure is not obtained the treatment can be repeated after 2 to 3 weeks

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Chapter XVI

NERVOUS AND MENTAL DISEASES

Diseases of the Nervous System

The idea that the diagnosis of organic disease of the nervous system can be made only by those specializing in neurophysiology, neuroanatomy and neuropathology is too generally accepted by many intelligent practitioners A neurological patient is often regarded as an unwelcome guest of doubtful behavior and rushed off to a consultant, not for the *confirmation* of a diagnosis, but to have one made Though the diagnosis of involved and complicated cases may demand the experience and skill of a specialist, there are many others which can be diagnosed and treated satisfactorily by the general practitioner, if he is conversant with the broad principles of neurological diagnosis and trains himself in the interpretation of the clinical manifestations of nervous disease

A *systematic examination* of the patient is more important in a neurological condition than in any other field of medicine Wechsler states "It may be conceded that no amount of method ever made a neurologist but it is equally certain that the want of it often marred one The scheme which one follows matters little but the method followed should have some order Two history and physical examination forms follow and are included merely as guides for those interested A brief examination of the nervous system should be a routine part of all physical examinations If the findings of this examination are negative, there is very little likelihood of there being a disease of the nervous system On the other hand, if abnormalities are found, further examinations can be made

Tracy Putnam (1) has summarized what this minimum examination should consist of in the following words 'An inspection of the patient, gait, facies etc, should be made Also palpation of the cranium and spine should be done The cranial nerves can be rapidly examined by noting the size and shape of the pupils and their reaction to light, the eye movements, facial movements, rough hearing tests and examination of the tongue movements The motor system can be tested by testing the strength of the grips watching the gait, inspecting muscles and performing finger to nose test Sensory tests other than the Romberg test are not necessary unless specific complaints or other findings indicate them The knee jerks ankle jerks and plantar responses should be tested'

If for no other reason, this chapter has been written to refute a common belief among practitioners of medicine, namely that the examination of the nervous system entails an elaborate technique and a knowledge of high sounding terms

NEUROLOGICAL EXAMINATION

Record No Date Ref
Name Address Age Race Occupation

Chief Complaint

Symptoms Cranial—headache vision diplopia hearing vertigo speech

Upper Limb loss of power pain numbness tingling dragging or loss of control useless shakiness fine or coarse tremor writing difficulty involuntary movements (describe)

Trunk pain or stiffness in spinal column radiates
constant intermittent effect of weather exercise
pain in trunk numbness tingling sphincter symptoms potentia

Lower Limb loss of power pain numbness tingling stiffness unsteady gait

Other vomiting nausea
night blindness cushion or girdle sensation
constipation insomnia
anxiety tics
Flashes to R or L half of visual field
animals or people moving in homonomous halves
bad smell bad taste
dazed condition smack lips—jaws

Cerebrum Frontal memory disposition habits orientation

Temporal aphasia hallucinations of smell taste
dream states losing sight of medial lateral part of object

Parietal (Sensory) paresthesia touch pain temperature muscle sense astereognosis
(Motor) convulsion twitch intention tremor weakness or paralysis of muscle groups

Cerebellum Romberg 1 2 3 4 0 Ataxia Nystagmus (vertical—lateral)
F to N F to F H to H H to K T to T

Gait Spastic hemiplegic scissors ataxic drunken dancing waddling steppage festinating atasia—abasia marche a petite pas propulsion hyper extend knee joint automatic associated movements

Cranial Nerve Examination

Right	1st Cranial	Left	Right	VII	Left
	Wintergreen			Taste Ant ⅔ tongue	
	Camphor			Nasolabial fold	
	Menthol			Chvostek s Sign	
	Coffee			Lagopthalmos	
	II			Hyperacusis	
	Fundus			**VIII**	
	Fields			Watch tick	
	III IV VI			Audiometer	
	Ptosis			Barany	
	Nystagmus			Cochlear	
	Strabismus			**IX—X**	
	Extraocular movements			Palate deviation	
				Swallowing	
				Vocal cords	
	Pupils			Pul e rate	
	Size			Breathing	
	Shape			Aphonia	
	Light			**XI**	
	(Slow—Prompt—Thru small—large arc)			Sternomastoid	
	Accommodation			Trapezius M	
	Crossed			**XII**	
	Convergence			Deviation tongue	
	V			Atrophy of tongue	
	Jaw deviation			Pressure against cheek	
	Masseter palp			**V—VII—IX—XI**	
	Corneal (V—VII)			Hippopotamus	

Touch—Pain—Temperature

VII
Frown
Raise eyebrows
Shut eyes
Whistle
Blow out cheeks

West Register Street
Irish Constabulary
Hand grip
Rapid finger movement
Tap foot rapidly
Button coat eyes closed
Figure of 8 in air (foot)

Motor System

Head Fixation — Retraction
Ability to bend forward — Backward — *Sidewards*
Resistance to passive movements
Exostoses — Defects

Upper Limbs Atrophy of thenar — hypothenar — intrinsic muscles

Fingers Flexion
Extension
Abduction
Adduction
Thumb to finger tips
Grip Power — Quick release

Wrist Movement at wrist joint
Pronation and supination

Elbow Flexion — Extension

Shoulder Movement upwards — Forwards
Movement downwards — Backwards
Rotation of the joint

Pectoralis Major M Pt presses hands together in front of him

Latissimus Dorsi M Arms pressed downward against resistance being extended in horizontal position edge felt easily contracts on cough

Serratus Magnus M Winging of scapula on standing position with arms at sides Hands extended forward horizontally Leaning on either hand

Deltoid M (Lift extended arm outward to horizontal position test strength)
R — L

Brachio Radialis M (Bend arms against resistance fist closed thumbs up)
R — L

The Trunk

Erector Spinae M Able to stoop — Crawls up on self — Bends knees ad maximum with erect trunk to pick up objects (Patient face downward raises head and shoulders against resistance on his head)—are muscles seen plainly?

Abdominal Muscles
Deviation of umbilicus (Pt on back raises head)
Abdominal wall bulge on cough
Ability to rise from lying position to sitting without use of arms

Diaphragm
Epigastrium bulge or drawn in on abdominal respiration

Lower Limbs Foot deformity
Peculiar posture
Flexion contracture
Movements at Toe joints
Ankle joints
Knee joints
Hip joints
Kernig's Sign — Brudzinski sign
Atrophy
Fibrillary twitch
Tonus

Involuntary Movements
Tremor
Dystonia
Fibrillary contraction
Choreatic
Spasms Tonic
Myoclonus
Hemiballismus
Athetosis
Tics
Clonic

Right	Reflexes	Left	Right	Reflexes	Left
	Corneal—Cr V–VII			Cremasteric L 1–2	
	Jaw Cranial V			Bulbocavernous S 2–4	
	Biceps Br C 5–6			Anal S 5	
	Triceps C 6–8			Babinski L 4–S 2	
	Supinator C 5–6			Patellar clonus	
	Hoffmann C 6–T 1			Chaddock	
	Patellar L 2–4			Oppenheim	
	Reinforced			Gordon	
	Ankle clonus			Schaeffer	
	Int Hamstr L 4–S 2			Rossolimo	
	Ext Hamstr S 1–3			Flexion 4 L–S 2	
	Epigastric T 8–9			Dorsocuboidal	
	Mid abdom T 10–12			Ciliospinal	
	Hypogastric T 12–L 1			Palmomental	

Remarks

SENSORY EXAMINATION

	Pressure	Touch	Pain	Vibratory	Joint	Position	Temperature
Eye							
Face							
Arms							
Fingers							
1 C–1 D							
2 D–1 L							
L 1–S 5							
Epigastric							
Iliac Spine							
Testicle							
Sacrum							
Legs							
Toes							
Other							

Anesthesia (Describe)
Hypesthesia
Hyperesthesia
Paresthesias
Analgesia
Hypalgesia
Hyperalgesia

Summary of Present Illness with Positive Findings

Diagnosis

Recommendations

DIAGNOSTIC PROCEDURES IN THE CASE STUDY OF DISEASES OF THE NERVOUS SYSTEM

I Lumbar Puncture

Indications

1 Diagnosis and treatment of acute or chronic inflammations of the meninges
2 The diagnosis and treatment of meningism
3 The diagnosis and treatment of head injuries
4 The diagnosis of diseases of the central nervous system in which the clinical signs and symptoms are not themselves diagnostic
5 The management of syphilis

Contraindications

1 When the puncture would have to traverse infected skin or tissue
2 When the diagnosis is obvious and no additional information of therapeutic value can be obtained (Brain tumors with papilledema)
3 Neurological evidence of an expanding lesion in the posterior fossa of the skull with or without papilledema

Technique The best needle to use is one with a No 20 or No 22 gauge and a three way stop cock soldered to it The stylet should be long enough to extend through the stop cock The stop cock makes it possible to determine accurately the cerebrospinal fluid pressure without losing any of the fluid A good manometer is the Fremont Smith modification of the Ayer water manometer

The purpose of the puncture and the information which it is desired to obtain should be carefully considered before it is performed, in order to avoid repeating it needlessly The patient should be reassured while being prepared and placed in the proper position He should lie on the left side with head bent forward, knees drawn up and the back arched The plane of his back should be vertical to the floor It is useful to get him to clasp his hands behind the knees He should be comfortable and relaxed The level of the external occipital protuberance should be in line with the lumbar spine An area at least one foot square should be prepared over the lower half of the back with its center at the third fourth or fifth lumbar spine Soap and alcohol followed by iodine or merthiolate are used to prepare the skin The hands are scrubbed with soap and dipped in alcohol Gloves are not necessary if the hands are properly scrubbed Make a thumb nail mark in the space between the third and fourth or fourth and fifth lumbar spines Infiltrate the skin with sterile 2 per cent novocaine, using a small hypodermic needle a larger and longer needle is then inserted and the deeper tissues carefully infiltrated with 3 or 4 c c of the novocaine solution Wait a few minutes before inserting the spinal needle

Using the thumb nail mark as a guide, the spinal needle is inserted through the selected inter vertebral space the needle being grasped firmly at the hilt by the right hand and guided over the left thumb After the skin has been punctured the needle should be realigned and pushed deeper carefully holding the shaft of the needle by the left hand the back of the hand being pressed firmly against the patient s back to prevent the needle from going too far when the ligamentum flavus is pierced As the ligament is penetrated a slight give is felt by the fingers The stylet should be withdrawn in order to determine whether the needle is in the subarachnoid space If no fluid appears the needle should be pushed a few millimeters farther when a sensation of give may be felt by the guiding finger due to puncturing the dura If no fluid appears the needle should be rotated slightly or the position of its point changed since it may have become blocked by a film of the arachnoid tissue or by a

DATE & EXAMINATION ____________

R CRANIAL NERVES L	R MUSCLES L	R REFLEXES L	R COORDINATION L
I. Wintergreen	Masseter Cr. V	Corneal Cr. V & VII	F N T.
Camphor	Temporal Cr. V	Sucking Cr. V & VII	F F T.
II. Fields	Pterygoid Cr. V	[illegible] Cr. & VII	[illegible] T T.
III, IV, VI Ptosis	Forehead Cr. VII	Pharynx IX-X & XI	H-K-T.
NYSTAGMUS	Eyelids (closing) Cr. VII	J Cr. V	Adiadokokin.
OCULAR MOVEMENTS	Mouth Cr. VII	Biceps br. C5-6	Dysmetria
PUPILS	Platysma Cr. VII	Triceps C6-8	R GAIT L
Size	Soft palate	Supinator C5-6	Ataxic
Shape	Pharynx Cr. X-XI	Hoffmann C6-T1	Spastic
Position	Sternomast. Cr. XI & C2-3	Pectoral C6	Steppage
REFLEXES	Trapez. Cr. XI & C3-4	Mayer C6-T1	Limping
Light	Tongue Cr. XII	Wartenberg C6-T	Shuffling
Consensual	Diaphragm C3-5	Patellar L2-4	Propulsive
Convergence	Lev. scap. C3-5	Reinforced	Waddling
VIII. Tick	Rhomboid C4-5	Achilles L5-S2	Festination
VII, IX, X. SALT	Scapular C4-5	Reinforced	R STATION L
Ant.	Serrat. ant. C5	Clonus (ank.)	Romberg
Post.	Pectoral C5-T1	Int. ham. L4-5	One foot
SOUR	Deltoid C5-6	Ext. ham. S1 2	Trunk
Ant.	Latiss. dorsi C6-8	Epigast. T5-9	STEREOGNOSIS
Post.	Biceps C5-6	Mid-abd. T?	R TREMOR L
SWEET	Brachialis C5-6	Hypogast. T12-L1	REST
Ant.	Triceps C6-8	Cremast. L1 2	STATIC
Post.	Brachio. rad. C5-6	Bulbocav. [illegible]	MOVEMENT
BITTER	Flex. wrist C6-T1	Anal S-5	RATE
Ant.	Ext. wri. C6-8	Babinski L4-S1	AMPLITUDE
Post.	Pronators	Gordon	Eyelids
SPEECH	Ext. fingers C6-T1	[illegible]	Lips
Aphasia	Flex. [illegible] C7 T1	Chaddock	Tongue
Dysarthria	Flex. long. poll. C7 T1	Rossolimo	Hands
Scanning	Opp. poll. C8	Mend.-Bech.	Arms
Slurring	Hypothenar C8	Oppenheim	Legs
Stammering	Interossei C8-T1	Schäfer	MISCELLANEOUS TESTS
	Back	[illegible]	Kernig
	Upper abd. T6-9	[illegible]	Lasègue
	Lr. abd. T L1	R NERVES L	[illegible] Patrick dex.
	Glut. max. L4-S2	TENDERNESS	Trunk-thigh
	Psoas L2-4	SIZE	Chvostek
	Quadric. L2-4	CONSISTENCY	Myotonia
	Int. hamstr. L4-S1	Ulnar	
	Ext. hamstr. S-2	Median	
	Adduct. L2-4	Radial	
	Abduct. (glut. med.) L4-5	Sciatic	
	Rot. int. L4-5	Peroneal	
	Rot. ext. L4		
	Calf L4-S1		
	Ant. tib. (evert, inv.) L4-5		
	Post. tib. (invert.) L4-5		
	Peroneal (evert.) L4-5		
	ext. hal. L4-S1		
	ext. dig. L4-5		
	R SENSATION L		
	Head		
	Upper extremities		
	Thorax		
	Abdomen		
	ankle sacrum		
	Lower extremities		

nerve root No more than three trials should be made through one inter vertebral space Once the fluid has been obtained the right hand should turn the stop-cock to neutral in order to prevent the loss of fluid The manometer can now be attached The patient should be told to relax which is facilitated by having him pant several times The first pressure reading should then be taken Pressure readings taken during or after the following procedures are of diagnostic importance

1 Abdominal pressure with the flat of the hand
2 R jugular compression for ten seconds *then allow ten seconds for the fluid to* reach the base line
3 L jugular compression
4 Bilateral jugular compression
5 Straining down with the mouth closed and the breath held
6 *After each 5 c c of fluid has been re*moved
7 After the total amount has been removed

Interpretation A prompt rise in fluid pressure upon abdominal compression proves that there is free communication between the lumbar sac and the *manometer* Normally on compressing the jugular veins for ten seconds there is an increase of *from 150 to 300* mm of water pressure depending upon the degree of the compression Upon releasing the compression the pressure should *fall* within ten *seconds to or within a few* millimeters of the original level A comparison of the figures obtained by unilateral compression of each jugular vein is of value only in cases of lateral

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(Underline if egative)

Consciousness Inte ligence Memory Emotion Attention Cooperation Trophic Vasomotor Dysplasia Endocrine Dyskinesia Breathing S lowing

Pulse-carot d subclavian radial post.-tib dors.-ped. ercussion tenderness racked-pot note Bruit Stiff eck Head lting Sphincters

UE AL CONSULTATION

sinus thrombosis, since there is great variation in the size of the intracranial venous sinuses When jugular compression *fails to give a rise in* pressure or when upon the release of pressure the rise or the fall is delayed *subarachnoid block* is suggested This test is called the *Queckenstedt test* Confirmatory tests should be made In complete or partial block abdominal compression should give a normal response which in partial block is greater than the response to jugular compression An apparently normal response to jugular compression may occur in spite of complete spinal subarachnoid block if the patient holds his breath or strains during the compression

In some cases in which even after careful jugular and abdominal compression the presence or absence of block cannot be determined,

combined lumbar and cisternal puncture may be performed Abdominal and jugular compression should again be tried and the responses in the two manometers compared If at every test the levels are equal *there is no block* In the presence of block jugular compression gives a better response in the cisternal manometer, while abdominal compression gives a better response in the lumbar manometer Also the removal of fluid from either locus results in a pressure drop in the corresponding manometer, but no drop, or perhaps a delayed drop in the other manometer depending upon whether the block is partial or complete In a normal case the removal of fluid from either locus would result in a parallel drop in pressure in both manometers A marked fall in pressure caused by the removal of a small amount of fluid, indicates a small reservoir such as in subarachnoid block or in expanding lesions of the cerebral hemispheres A slow drop in pressure upon the removal of large amounts of fluid indicates a large reservoir such as would be present in hydrocephalus meningitis and meningism

If an *elevated pressure* is found fluid should be removed slowly and in sufficient amount for all tests (12 c c) Every specimen of fluid should be subjected to the following routine examinations

1 Color
2 Cell count
3 Globulin
4 Total protein
5 Colloidal gold curve
6 Wassermann test

If the cell count is elevated the following are indicated

1 Staining of centrifuged specimens for microorganisms
2 Cultures and on certain occasions animal inoculations
3 Sugar

When the desired amount of fluid has been removed the needle should be withdrawn quickly and a dressing applied No collodion is necessary but the area over the puncture can be massaged to aid in its closure It is unnecessary that the patient should be on his stomach for at least six hours then on his back for from twelve to twenty four hours Studies on inductees into the Armed Forces (47) have shown that rapid collection of spinal fluid and maintenance of the erect position after spinal puncture is both safe and such a practice is accompanied by less than 1 per cent of post puncture headache This is believed to be due to the more nearly normal intracranial pressure maintained by the erect position thus preventing oversecretion and compensatory hypertension with headache It is said that increasing the fluid intake will cut down the incidence of post puncture headache It has been definitely shown that the use of small bore spinal needles is accompanied by fewer post spinal headaches than when the larger bore needles are used Notwithstanding what most texts say concerning this question there is no reason to impose the expense of an extra hospital day on a patient merely because he has had a spinal puncture The writer has seen scores of patients enter dispensaries merely to receive a spinal puncture immediately afterwards get up and go their way without any serious after effects such as headache, etc

II Cisternal Puncture

Cisternal puncture is valuable in conjunction with a puncture in the lumbar area to determine whether there is a subarachnoid block present, and for the injection of lipiodol or air Post puncture headache is not a hazard in this procedure and the patient can go home immediately after the puncture has been made It is not used as frequently as spinal puncture, and is not a procedure for those not skilled in its technique

Procedure The patient is placed in the lateral recumbent position with the head flexed sharply on the chest A small pillow is placed under the head in order to maintain the thoracic and cervical vertebrae in the same horizontal plane The skin in the midline on the back of the neck is shaved and prepared with iodine almost to the external occipital protuberance Under aseptic precautions and after donning gloves the thumb of the left hand locates and covers the external occipital protuberance one inch below which a skin wheal is raised with novocaine The point of the needle should be slightly blunt and its shaft should have a mark or a small piece of rubber at a distance of 7 5 cm from the point The needle is inserted through the wheal and is directed

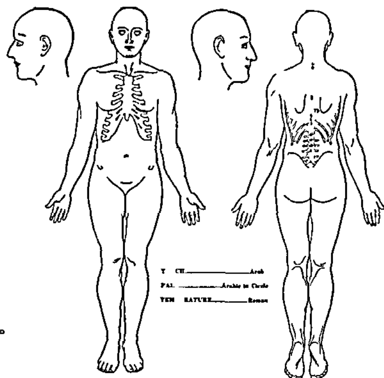
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Pulse-carot d ___ subclavian ___ radial ___ post.-tib ___ dors.-ped. ___ ercussion tenderness ___ Cracked-pot pain ___ Bruit ___ Stiff neck ___ Head tilting ___ Sphincters ___

SURGICAL CONSULTATION ___

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II Cisternal Puncture

Cisternal puncture is valuable in conjunction with a puncture in the lumbar area to determine whether there is a subarachnoid block present, and for the injection of lipiodol or air Post puncture headache is not a hazard in this procedure and the patient can go home immediately after the puncture has been made It is not used as frequently as spinal puncture and is not a procedure for those not skilled in its technique

Procedure The patient is placed in the lateral recumbent position with the head flexed sharply on the chest A small pillow is placed under the head in order to maintain the thoracic and cervical vertebrae in the same horizontal plane The skin in the midline on the back of the neck is shaved and prepared with iodine almost to the external occipital protuberance Under aseptic precautions and after donning gloves the thumb of the left hand locates and covers the external occipital protuberance one inch below which a skin wheal is raised with novocaine The point of the needle should be slightly blunt and its shaft should have a mark or a small piece of rubber at a distance of 7 5 cm from the point The needle is inserted through the wheal and is directed

TABLE LII

The Cerebrospinal Fluid in Differential Diagnosis

Disease	Initial Pressure (Horizontal Position) mm of spinal fluid	Appearance	Cells per cmm	Protein mg per 100 cc	Sugar mg per 100 cc	Chlorides (as NaCl) mg per 100 cc	Colloidal Gold	Comment
Normal: Lumbar Cisternal Ventricular	0 to 180	Clear Colorless No clot	0 to 5 0 to 5 0 to 3	15 to 45 10 to 25 5 to 15	50 to 80 50 to 80 55 to 85	710 to 745	0000000000	Sugar and chloride values apply to fasting nonfebrile individuals with normal blood values
Meningismus (75 cases)	Normal to 500+	Normal	Normal	5 to 45 usually low	50 to 100	620 to 750	Normal	Excess of clear fluid with low protein content. Chloride reduction due to lowering of blood chlorides
Acute Purulent Meningitis (164 cases)	200 to 750+	Opalescent to purulent Faintly yellow color Coarse clot	500 to 20 000 chiefly polys	50 to 1500	0 to 45	575 to 700	Variable rarely fir t ne	Pressure increased unless subarachnoid block develops. Rare cases with cell count below 100 or above 40 000. Sugar content practically always reduced although normal values may be found early in disease. Extreme chloride value 477 to 760 average 650. Organisms found in clot or sediment culture positive
Tuberculous Meningitis (84 cases)	150 to 750+	Opalescent (rarely turbid) Faintly yellow color Delicate clot	25 to 500 chiefly lymphocytes	45 to 500+	0 to 45	525 to 675	Usually midzone or normal	Pressure nearly always increased unless subarachnoid block develops. Rare cases with cell count under 10 or over 2 000. Five to 25% polys usually present, rarely over 50%. Extreme sugar values 0 to 59 usually falling progressively. Extreme chloride values 470 to 732 usually falling progressively, average 600. Values below 650 in most cases. Tubercle bacilli found in clot or sediment. Guinea pig inoculation positive
Acute Syphilitic Meningitis (untreated) (80 cases)	130 to 600 usually increased	Clear to turbid Colorless or xanthochromic Clot often present	25 to 2 000+ chiefly lymphocytes	45 to 400	18 to 84 Normal (50%) Decreased (50%)	635 to 745 usually slightly decreased	F t zone (40%) M dzo e (55%) Normal (5%)	Rarely less than 25 cells. One to 20% polys usually present, rarely over 50%. Cerebrospinal fluid Wassermann positive in 85% (blood Wassermann positive in 60%). Difficult to differentiate from tuberculous meningitis, brain abscess and occasionally from acute poliomyelitis. me g t W m ll id l g ld hl d s d ult mpo ta t

D m t a P lyt c (u t ted)	100 t 300	Norm l Clot ra ly p es t	15 to 150+ ch fly lymphocytes	50 to 150	Norm l	N rm l	F t zone	C b osp n l fl d Was rma po t e e n d l t s f 0 l cc ne ly 100% f unt ted c es Blood W man pos ti n 80 to 90% Cells m y r h 400+ wh n ssoc ted w th m gitis Prot occas ally 200+ S gar ly decreased Ce eb osp n l fl id find ngs ot path gn mo c f dem t a paralyt They may oc r in y f rm f eu osyph l
T bes D l (t t d)	N m l	N rm l	10 to 80+	5 to 100+	N rm l	N mal	M d e or f t e	C r b p l fl d find gs depe d on d gree f accompa y g m g t W erm p c t lly al y pos t in c b osp l fl d of rly u t ated ses N mal fl d n t o comm in t ted or lat bu nt-out c es
V cul r N yph l (C r br l Th mbos Syph l) (74 cases)	Norm l (80%) 00 to 400 (20%)	Norm l	6 t 100 (55%) No m l (45%)	45 t 150 (70%) N mal (30%)	N rm l	N m l	N m l (35%) F r t z e (15%) M d e (50%)	C bro p l fl d f d gs d pe d on d g ee f accomp y g m g tis Fl d n rm f in p v c l r n osyphil s Blood W e m po ti e in 80% ce eb o r nal flu d Wass m n po ti 50%
A pt M geal Re c t (B Ab ss) (S us Th mbo s) (E tr d ral Absce s t) (85)	1 0 t 750+ ally inc e s d	Cle cl dy or t rb d M y be antho ch om c M y ha e cl t	U u lly 5 to 500 O ally 1 000 t 10 000	20 t 200+	35 to 110 u u lly mal	600 to 750	V r able	Cha ges in fl d repres t men ng l r ct on t a ept c fo s in the cran m ch s s th mbo s ext d ral abs es eptic mbol s, a d brain ab or to an a ea of s ft g near the ve t l as re lt of hem h g th om b s s r o pt c mbolus P re usu lly h gh t in brain b ess C ll o t ar es f m few cells (5 or less) to s al thousand P e to 10% polys p ct lly always p es t In c s with high c ll u t polys ally pre dominate N m l or o ly l ghtly lo ed sug r d ff r tiates it f m b ter l men ng t
A t A t P l o- myel t s (116 ca e)	Us ly m l	C e r or sl ghtly op les t Colo less or f ntly yell w D l cate clot may be p esent	10 t 500+ h fly lymphocyt s	20 to 350 often p g rease	50 t 100	670 to 750	N rmal or m d zone	P re usu lly mal rarely r 300 (may reach 700) C ll o t us lly u d 300 rarely n m l h ghe t d ring r pa lyt c tage when ally 2 000+ Poly rarely p ed m i ate Cells us lly h w progres i e de h le p te ally sto s pr g s f r t t t o to three eeks
Ep demic E c ph l t s	N m l r sl ghtly in c sed	N m l	0 to 100 lymph ocytes (l most lu si ely)	20 t 75 lly m l	50 t 100	Normal	N bl	P es es usu lly m l o er 250 ext em ly rare c ll l n e sually m l l b t cou ts l gh as 800 may oc ur Polys lm t Normal sugar and chl de d ff t te t f om tuberculous m ng t Normal pre s re d fferentiates it f m b n t mor or abscess

TABLE LII—*Continued*

Disease	Initial Pressure (Horizontal Position) mm of spinal fluid	Appearance	Cells per cmm	Protein mg per 100 cc	Sugar mg per 100 cc	Chlorides (as NaCl) mg per 100 cc	Colloidal Gold	Comment
Postinfectious Encephalomyelitis	80 to 450 usually increased	Normal	0 to 100+ chiefly lymphocytes	15 to 75	50 to 100	640 to 750	Normal or slight change	Pressure usually increased Cells rarely exceed 50
Herpes Zoster	Normal	Normal	0 to 500 usually increased	0 to 110	Normal	Normal	Usually normal	Cells are practically all lymphocytes They appear early and persist for several weeks Protein increase may persist for several months
Mumps Meningitis	Normal slightly increased	Normal or opalescent	0 to 2 000+ chiefly lymphocytes	20 to 125	Normal	670 to 750	Usually midzone	Lymphocytes increased in most cases of mumps even in the absence of meningeal signs
Brain Tumor (Subtentorial) (49 cases)	150 to 800+ usually above 220	Clear Occasionally xanthochromic)	Normal (80%) 6 to 25 (15%) 26 to 150 (5%)	30 to 500 (see comment)	50 to 100+	690 to 750	Variable Normal (30%) First zone (10%)	Tumors of the brain stem usually have normal pressure Protein in acoustic neuromas nearly always high (100 to 500 mg) fluid often xanthochromic Cerebellar tumors usually have normal or only moderately increased protein (20 to 100) Ventricular protein normal in subtentorial tumors Cells chiefly lymphocytes Partial block often present
Brain Tumor (Supratentorial) (116 cases)	150 to 800+ usually above 220	Clear Occasionally xanthochromic	Normal (70%) 6 to 25 (20%) 26 to 150+ (10%)	20 to 2 000 (see comment)	50 to 100+	650 to 770+	Variable Normal (40%) First zone (2%)	Pressure may be normal especially in pituitary early or degenerating tumors Cells rarely 1 000+ chiefly lymphocytes If ventricle not invaded protein is usually normal in ventricular and lumbar fluids I u l t ral tumors invading ventricle lumbar fluid and fluid from involved ventricle have sed protein and are lly xanthochromic C tr l t l ventricular fluid normal I tumors of the 3d t l d c rp s callo m l mb fl d d fluid from both lat l t l s u lly xanthochromic with r d p ot

C d Tum Sp n l S b h d Bl k (37 c s)	ꟈ rmal lo (omm nt)	Cl r C l l or xa thoch m Clot oft p es t	Norm l (60%) 6 t 100 (40%) Ch fly lymph ocyt	36 to 45 (15%) 46 to 3 500 (85%)	50 to 100	650 to 750	Va ble	C mpl t r p t l b h o d block prac t lly lways pre e t Comb ned l mba d tern p t es l able co frm g p t al bl ck Y ll w fl d th h gh p ote n o te t m y how spo tan lott g Dy mic bl k bed m t at d ca d q t mor o ly hen p t re s b lo v l l of t mo b t pro tein early l ay s ı ased Bl k m y t in P tt d seas fractu or d l ation of rt b te d hron c m ing t epıd al b c ss t Wh bl ck d t ı f t cell t m y be m k dly reas d and poly m y p edom te
U m a (46 c ses)	90 t 600+ u lly d	N m l r l ghtly yell	N m l (75%) 6 to 40 (25%)	0 to 45 (50%) 46 t 100 (50%)	50 to 150	V ble (25 to 915	V ble	Urea d np te itro re s d n blood a d bro p l fl ı l Chlor d e l w 30% ele t d 10% lues bo e 70 re rarely f d n any th r cond t
Ce eb l Th omb s (A te cl t) a d N ptic Emb l (50 c)	Normal (75%) 180 t 400 (25%)	N rm l (85%) Xanth h m (15%)	Normal (75%) 6 t 50 (25%)	N m l (60%) 46 t 100+ (40%)	50 to 100	680 t 750	N rm lor ra ely l ght h g	P es o 300 ar ra C lls lly b low 10 r ly 400+ P t ıs ra ly o e 100
C b l Hem h g (50)	180 t 300 (40%) 300 to 1 100 (40%) N rm l (20%)	N m l (15%) Bloody (75%) X tho h om a W tho t rbc (10%)	M y r d cells (75%) (mme t)	20 t 2 000 ally ın c d	50 t 100	640 t 750	V ble	N nbl dy fl ds m y l w m k d pleocyt s (300 t 3 500 p lys) d e t pt c me g l act o S k occa lly dec d at onset ın es
S ba h id Hemo rh ge (36)	110 to 700+ usu lly d	U fo mly bloody Xanth ch m N l t	M y cre ated red bl d ll (comm t)	20 to 1 000+ lly c e d	50 to 100	680 to 750	V bl	P ogre e f ll p essu e d dec e s numb f d blood cell p ated p ct Yell w lor app g w th f h of t ı creas s f f t to tend y th de creases R e show lo s g r at onset Ra ely m k d ı cre se n p ly (5 000+) o ally a sociat d w th l ugar
Ce eb l T m	0 to 1 100 su lly e d	Bloody Xanth ch om c O lly mal	Usu lly ma y r d bl od cells	20 t 1 000+ u ually ın c d	50 to 100	N m l	Var able	Fl ıd usu lly n mal concuss but early al ays bloody l e b aın ıs c t d r lace t d P e re m y occas lly be l v as r lt f s ırg al sh k o d l tears
S bdu al H m t ma (34 c)	180 t 600+ (80%) N mal (0%)	N mal bl dy th h	N m l m y d bl d cells	20 t 1 000	50 t 100	Nor al	Va ı ble	Flu d lly blo ly f p ctu e s p formed ft y y Prote n l gh n bl ody fluıd b t mal or l ghtly le ated (0 to 75) ın l ar or yellow fluıds

TABLE LII—*Concluded*

Disease	Initial Pressure (Horizontal Position) mm of spinal fluid	Appearance	Cells per cmm	Protein mg per 100 cc	Sugar mg per 100 cc	Chlorides (as NaCl) mg per 100 cc	Colloidal Gold	Comment
Bloody Tap	Normal or low	Bloody with clot. Supernatant fluid *colorless*	Many red blood cells	Normal or increased	Normal	Normal	Normal unless red blood cells over 20 000	Variation in amount of blood in different tubes. Clotting occurs except when only few red blood cells are present. Supernatant fluid is colorless unless over 100 000 red blood cells, pink if hemolysis occurs. Approximately 1 white blood cell added with every 500 red blood cells and 1 mg of protein with 1 000 red blood cells
Epilepsy (620 cases)	50 to 200 (90%) 200 to 250 (9%) 250 to 300 (1%)	Normal	Normal	Normal (87%) 46 to 85 (13%)	50 to 90	700 to 750	Normal	Suspect brain tumor when pressure persists above 200
Multiple Sclerosis (100 cases)	Normal	Normal	Normal (70%) 6 to 40 (30%)	Normal (75%) 45 to 130 (25%)	50 to 90	700 to 750	Normal or slight change (50%) First zone (25%) *Midzone (25%)*	Pressure rarely exceeds 200. Slight lymphocytic pleocytosis in 30%. A first or midzone gold curve in an otherwise normal or nearly normal *fluid with negative blood and cerebrospinal fluid* Wassermann in a patient not previously treated for syphilis is strong evidence for multiple sclerosis
Polyneuritis (145 cases)	Normal. Occasionally increased	Normal. Occasionally xanthochromic	Normal. Occasionally increased	20 to 1 500 (see comment)	50 to 100	670 to 750 (rarely lower)	Variable	Cases associated with alcohol, lead or triorthocresyl phosphate (ginger paralysis): cells 6 to 25 (8%), protein 46 to 5+ (25%), rarely slightly yellow. Cases associated with acute infections, diphtheria, syphilis, malignancy and of unknown etiology: cells 6 to 165 (25%), protein 46 to 100 (30%), 100 to 1 500 (30%). With increased protein fluid is often xanthochromic, rarely *clots spontaneously. Colloidal gold* may show any type of curve. Pressure occasionally increased to 400+
Lead Encephalopathy	*Increased*	*Normal or* slightly yellow	*Increased, usually* lymphocytes	*Normal or increased*	*50 to 100*	*680 to 760*	*Variable*	*Pressure nearly always increased. Cells nearly* always increased, occasionally up to several thousand. Polys may predominate. Lead is present in the fluid

slightly upward until when advanced it strikes the base of the occiput The needle is then withdrawn a few millimeters its point depressed and directed a trifle lower If it again strikes bone, it is depressed slightly again after being withdrawn a little The atlanto occipital ligament yields with a snap or a sense of 'giving when it is pierced Bleeding and other difficulties are rare if one keeps to the midline The distance from the skin to the point of the needle in the cisterna varies greatly Usually it is from 4 to 6 cm but it may be up to 7 5 cm It is rarely advisable to advance the needle further than 7 5 cm The stylet of the needle is now withdrawn and should fluid appear is reinserted and the needle advanced another millimeter The medulla lies under the site of the puncture the needle therefore should be advanced cautiously The pressure is read with a manometer similar to that used in lumbar punctures When a sample of fluid is procured or the pressure readings obtained the needle is withdrawn quickly the iodine is removed from the skin with alcohol and if the puncture wound bleeds a small cotton pledget is applied with collodion

III *Encephalography and Ventriculography*

Skiagraphy of the brain after the cerebrospinal fluid has been partially replaced by air introduced through a lumbar or cisternal puncture is known as *encephalography* Upon entering the spinal subarachnoid space the air rises into the cisterna magna part going into the basal cisternae and the remainder into the fourth ventricle through the foramina of Luschka and Magendie then by way of the aqueduct and the third ventricle into the lateral ventricles The air thus displaces all the fluid in the ventricular system and the cerebral subarachnoid space Roentgen studies then made show with great clearness the outline of the ventricular system The procedure is not without danger and should never be used if there is a marked increased intracranial pressure

Indications

1 Obscure neurologic disorders in which it is believed that there is an expanding lesion of the brain
2 Spurling (2) believes all epileptics whether they show localizing neurologic signs or not should have encephalograms taken Many surgical lesions will be demonstrated and many otherwise hopeless cases will be benefitted
3 In cases with persistent headache from cerebral trauma introduction of air into the subarachnoid space often has a beneficial therapeutic effect

Contraindications

1 A high degree of papilledema
2 A lesion in the posterior fossa of the skull
3 An active inflammatory lesion of the meninges

Choice and Advantages of Each If the intracranial pressure is great ventriculography is advised instead of encephalography the ventricles being entered directly through bilateral trephine openings in the skull and air introduced after the ventricular fluid has been removed The advantage of encephalography over ventriculography lies in the fact that not only are the cerebral subarachnoid spaces and the basal cisternae rendered visible but when proper filling with air has taken place the sulci the outlines of the corpus callosum and of the tentorium cerebelli are seen as well

Technique of Encephalography The following technique is recommended as combining the best features of several methods

1 Lumbar puncture with complete study of the cerebrospinal fluid dynamics cytology chemistry and serology should always be performed before encephalography is attempted The information thus obtained may contraindicate encephalography or render it unnecessary *If the lumbar cerebrospinal fluid pressure is 200 mm of water or more while the patient is recumbent encephalography is contraindicated* The lumbar cerebrospinal fluid pressure in recumbency should be recorded for purposes of reference during encephalography

2 Deep narcosis or anesthesia is a boon to both operator and patient Inhalation anesthetics such as ether ethylene and nitrous oxide are to be avoided because they produce marked abnormalities of intracranial and systemic vascular pressures with greatly increased intracranial pressure Avertin (100 mg per

kilo of body weight per rectum) is effective in children The rate of injection should be very slow and the dosage depends entirely upon the patient's reaction during injection *Sodium pentothal* is used as a standard in adults (see von Storch and Karr)

Patients who have been taking barbiturates (epileptics, etc) do not react favorably to *avertin amytal, nembutal* and similar narcotics In such cases and in selected cooperative patients, *scopolamine* and *morphine* may be used Scopolamine hydrobromide ($\frac{1}{150}$–$\frac{1}{120}$ grain) should be given subcutaneously two hours preoperatively and morphine sulfate ($\frac{1}{8}$–$\frac{1}{6}$ grain) fifteen to thirty minutes preoperatively

3 The entire procedure from subarachnoid puncture to and including roentgenography should be performed with the patient in the sitting position The patient sits on a stool or chair with his back anteroflexed The use of one of the encephalographic chairs is recommended

4 Lumbar puncture affords the most efficient practical and safest means of obtaining a complete air replacement encephalogram The use of 2 lumbar punctures is advised for by such means only, can fluctuations in intracranial pressure be prevented The use of an automatic simultaneous replacement apparatus is especially convenient, for besides the above advantage the operator is free to attend to manipulation of the patient's head, etc The usual sterile technique is followed as in performing a lumbar puncture Free flow of fluid from both needles must be obtained before replacement is attempted if a prolonged troublesome procedure is to be avoided It is better to spend five minutes assuring oneself of free flow, than to spend thirty minutes adjusting and readjusting the needles apparatus and patient

5 Nitrogen, helium carbon dioxide and oxygen have all been used to replace cerebrospinal fluid but air is equally satisfactory

6 The amount of gas to be used is variable depending upon the size of the ventricles etc and hence cannot be standardized The amounts used should depend solely upon the pressures produced The pressure may be standardized in any individual or series of individuals When possible all available cerebrospinal fluid should be replaced by gas (i e gas instead of spinal fluid will flow from the needles)

7 Enough gas should be introduced while the patient remains sitting in order to produce a subarachnoid pressure at the lumbar sac approximately equal to atmospheric pressure

8 During replacement, the patient's head should be moved forwards and backwards from time to time in order to assist the air in rising to the cisterns and ventricles This maneuver is essential to the complete replacement of intraventricular fluid and without it the roentgenogram may show localized collections of gas which erroneously suggest atrophic areas Rotation of the head is unnecessary and lateral flexion should be avoided In lateral flexion unequal amounts of gas collect on one or the other side of the falx cerebri producing a picture simulating unilateral cortical atrophy Movement of the head results in a massage of the brain which has lost its supporting fluid cushion and therefore should be done very slowly and gently

9 The patient should be maintained erect for roentgenography Routine stereoscopic face forward (AP), right and left lateral exposures should be made as soon as possible after replacement The sooner the roentgenograms are taken the better especially when oxygen is used *In cases of suspected temporal lobe lesions* lateral stereoscopic views are taken with the patient recumbent and the suspected lobe uppermost The intern should be present to direct special views *In suspected occipital lobe lesions* exposures are made with patient lying face down on the casette Both of these recumbent positions are assumed after the erect pictures have been taken Exact centering of the patient s head for all pictures is essential The entire procedure may be wasted by failure to obtain true lateral and exact anteroposterior views

10 Post operatively the patient should be kept flat in bed for at least one or two days The *pulse blood pressure respirations* and *temperature* should be carefully observed for forty eight hours *Sedatives or ice bags* can be used to relieve the headache and the usual treatment for surgical shock should be instituted when necessary Subsequent lumbar puncture

for the release of air or reduction of increased intracranial pressure is rarely necessary because the air is rapidly absorbed and normal or decreased intracranial pressure is the rule *Fluids* should be given as desired

11 Much of the information given by a complete encephalogram may be gained by the 'bubble method but this usually shows only the ventricles, and may even fail to do that This method consists in making a cisternal puncture with the patient in the sitting posture 20–30 c c fluid are withdrawn and replaced by an equivalent amount of air The roentgenograms are then taken in the recumbent position The bubble of air outlines only the uppermost portion of the ventricles so that a number of views are necessary in order to outline the whole system Familiarity with the picture of complete filling is necessary for interpretation The resulting disturbance of the patient is however much less than that from complete fillings and the method is preferred in many clinics

12 Air encephalography besides causing the patient considerable headache is not without danger, and should not be undertaken without having a definite diagnostic objective in view Its value in treatment of traumatic headache is doubtful

In conclusion it must be said that a wide experience is necessary before the films can be properly interpreted it follows that *this work is done best in large clinics by those who are skilled* in the technique and are familiar with the abnormalities commonly met with

IV Lipiodol Myelography

Definition Radiography of the spinal subarachnoid space and structure outlined by it after the replacement of a small volume of cerebrospinal fluid by halogen oils

Indications (1) A lesion of the cord when complete or incomplete subarachnoid block has been demonstrated by lumbar or combined lumbar and cisternal punctures but in which the exact location and extent of the lesion causing the block cannot be determined by a careful neurological examination (2) Lesion of the cauda equina when subarachnoid block cannot be demonstrated

Contraindications (1) When the level and extent of the lesion is revealed by a neurological examination (2) A known inflammatory reaction of the cord or its coverings

Method The injection may be made in the ward or in the x ray department Lumbar puncture is performed in the usual manner The lipiodol is warmed to body temperature For visualization of block the dose of oil is 1 or 2 c c for visualization of the intervertebral discs the dose is 5 c c An equal amount of spinal fluid is removed before the injection of oil After injection the patient is kept sitting up until placed on the fluoroscopic table when he lie down The course of the oil is then observed in the fluoroscope as the body is tilted A high tilt, to almost 60 , is necessary in order to have the oil pass the normal thoracic curve Films are taken at appropriate intervals

Dangers The use of lipiodol should be restricted to those instances in which localization by neurological means is impossible, when air injection is unsatisfactory, or when it is proposed to perform a laminectomy (at which time the lipiodol will be removed) If there is incomplete block the patient s head should never be allowed to be lower than the pelvis Lipiodol may cause an inflammatory reaction in the cord nerve roots and along the perineural sheaths

V Pneumo Myelography

Definition Pneumo-myelography is the radiographic demonstration of the spinal subarachnoid space and structures outlined by it following replacement of the cerebrospinal fluid by air

Indications

1 The demonstration of the lower level of complete subarachnoid block
2 Demonstration of the outline of the caudal subarachnoid space

Contraindications With complete subarachnoid block above the lumbar region the demonstration is of little value

Method (1) Gas should be evacuated from the intestines as for a scout film of the abdomen (2) Nembutal 0 1 to 0 2 gram is given by mouth one hour before the procedure (3) Lumbar puncture is performed on the roentgen table After a careful check of the dynamics 2 c c of fluid are removed for the determination of total protein followed by the

removal of 5 c c for a second protein determination (4) The table is tilted until the head is higher than the feet and 40–50 c c of fluid removed (5) The table is then tilted so that the pelvis is 15° higher than the head, any available fluid is drained and replaced by an equal volume of air which is introduced slowly with a 50 c c syringe and a rubber tube connection The needle is then removed (6) The table is now tilted until the pelvis is 25° higher than the head and the appropriate roentgen exposures made Fluoroscopy is of no use in this procedure (7) The patient s pelvis should be kept elevated above the head, he should be returned to bed in the same position and kept so for twenty four hours

VI Electroencephalography

Electroencephalography has become widely accepted in neurological and psychiatric clinics At the present time it is in a stage comparable to the earlier phases of electrocardiography While exact interpretations of the physiologic significance of various portions of the specific types of brain waves have not yet been concluded equivalent to normal' tracings have been established and are of value

Electroencephalography is of practical value only as an adjunct to a thorough clinical study and when its results are positive It has its greatest use in the study and differential diagnoses of the epilepsies by means of the pathological rhythms obtained It does not give a characteristic tracing in every case of epilepsy yet such are at times obtained from those with a family history of the disease but who do not themselves suffer from it It has proven of great value in epileptic equivalents, psychomotor attacks and behavior problems in children The percentage of abnormal electroencephalograms in adult epileptics in the interval between attacks is about 80 per cent and is higher still (90 per cent) in children Abnormal tracings are fewer among adults with grand mal than among those with petit mal and psychomotor seizures The chance of finding abnormalities increases with the length of the record taken and the number of times the patient is studied Of the abnormalities only that of petit mal is absolutely specific of epilepsy and it is the only kind regularly precipitated by overbreathing Thus in the interval between attacks, the EEG will frequently provide no evidence of epilepsy and other confirmatory evidence will be necessary

With many of the types of abnormalities found the possibility of its being related to a psychopathic personality or to an old head injury must be taken into account Constitutionally predisposed neurotics, criminal delinquents and psychopaths may show abnormal EEG patterns In some cases, abnormal tracings have shown that the neuropsychiatric symptoms were probably due to a reduced supply of oxygen and dextrose to the central nervous system, the EEG tracings appeared to be modified by factors which improved the carbohydrate metabolism Cases of postconcussion syndrome have given abnormal waves Some workers have used the EEG to diagnose true from false blindness in hysterical patients, others have used it to follow the progress of neurosyphilis, paresis and the effect of treatment The EEG has proven of value in localizing brain tumors especially those in silent areas ' there being a focal dysrhythmia known as delta waves over the area of the tumor

It must be remembered that the EEG cannot detect loss of brain substance unless the mass of tissue which has been lost or destroyed is very large for what is recorded on the EEG is activity, and when a part of the cortex has died and ceased to function it is hardly missed in the great welter of activity that remains

The literature suggests the following diagnostic and prognostic values for the electroencephalogram

Epilepsy For diagnosis localization, prognosis and regulation of treatment i e the gauging of efficacy of anti convulsant drugs

Narcolepsy For diagnosis

Brain Tumor For diagnosis and localization

Subdural Hematoma For diagnosis and localization

Brain Trauma Diagnosis localization and prognosis

Meningitis For prognosis (residuals)

Brain Abscess For diagnosis and localization

Encephalitis For diagnosis and prognosis

Sydenham's Chorea For prognosis (cortical involvement)
Schilder's Disease For diagnosis
Behavior Disorders For diagnosis and prognosis

Other Uses It has been shown that in schizophrenia dysrhythmias are frequent While formerly it was believed that manic depressive psychoses were associated with an increase in the alpha index recent work has shown that this is not necessarily true

VII Roentgenograms of the Skull

Stereoscopic films are desirable in the x ray study of the skull by such films it is possible to examine the interior of the skull both inner and outer tables and the base as well as such areas of calcification as may occur normally or as may be seen in certain tumors The only *areas where calcification may occur without clinical significance* are the pineal gland the falx cerebri and the choroid plexus The pituitary fossa and its clinoid processes are best seen in stereoscopic views An increase in the intracranial pressure of long standing may be recognized by the digital markings of the bone Atrophy of the inner table conforming to the convolutions of the brain may be disclosed Such markings are most prominent in the squamous portion of the temporal bone and in long standing cases involve the entire inner table of the skull

Tumors growing from the meninges may give rise to bony changes One should learn to recognize normal and abnormal variations in the sella turcica thinning of the vault due to chronic disease or pressure erosion and localized deposition of bone due to disease or tumor The vascular markings of the skull deserve special study for they are subject to great variation in normal persons though a localized increase in the middle meningeal channel on one side may be the only clue to a meningeal growth it may be due simply to a vascular malformation Erosion of the overlying portion of the skull may appear in tumors arising from the meninges If the tumor is large both tables may be eroded the growth then forming a bulging mass beneath the scalp

Metastases Carcinomas of the breast thyroid prostate sarcomas and hypernephromas metastasize to the skull and cause destruction of the bone Bone destruction is not accompanied by the abnormal vascular markings seen in cases of meningeal tumor

VIII Roentgenograms of the Spine

Stereoscopic films in the antero posterior and lateral positions should be taken as these will permit a careful study of the vertebral processes laminae bodies and intervertebral spaces *Destructive lesions of the bodies or disks and arthritic processes may often be more clearly shown on lateral than on antero posterior films* One should look for *wedging* of the collapsed vertebrae *eroded areas* such as are seen in neoplasms and *irregular calcifications* resulting from inflammatory conditions *Widening of the vertebral canal or intervertebral foramen* due to slow growing tumors may be seen One should hesitate to make a diagnosis of tumor solely upon the basis of increased intervertebral measurements unless definite destructive changes are present as there may be widening in fractures spina bifida and other anomalies of the spine

Interpretation of Skull and Spinal Roentgen Films Only those experienced in the field of roentgenology should attempt to interpret these films

EXAMINATION OF THE MOTOR SYSTEM

In patients with no complaint of muscular paralysis it is sufficient to observe the patient s *gait* his *voice* and *facial expression*, any *abnormality of posture tremor* or *spasm* and to note the presence or absence of *associated movements, tics* and *involuntary movements*

The *power* of movement is then tested independently for each joint The earliest upper motor neuron weakness is found in the dorsiflexion of the wrist and ankle Careful attention should be paid to the nutrition of the small muscles of the hands and shoulder as these muscle groups are most likely to be involved in spinal cord disease such as *progressive muscular atrophy* and *syringomyelia* If the weakness involves the upper extremities the patient may state that he has difficulty in holding objects which drop from his hands or that he is clumsy in buttoning his clothing When weakness involves the lower extremity the patient may state that he drags his foot or

toes, that he stumbles or has difficulty in climbing or descending stairs

Before assuming that any paralysis or paresis exists, ankylosis and old fractures should be excluded as well as bursitis, and muscular and ligamentous strains When there is paralysis the state of the muscles whether *atrophic*, *hypertrophic* or *pseudohypertrophic*, should be determined

The strength of the muscles of the arms can be examined by testing hand grips, flexion and extension of the wrists elbows and movements of the shoulder joint The contractile power of the abdominal muscles may be estimated by observing them during a cough or by having the patient raise his head from the pillow without the aid of his arms The intercostals may be felt by the finger tips during inspiration, the diaphragmatic movements by percussion or fluoroscopy Movements of the spinal muscles are best observed by making the patient bend forwards and backwards after being stripped to the waist In *Parkinsonism* the power of resisting passive movement is strong while the speed and extent of movement is lessened by the rigidity of the muscles In *hysteria* the patient performs movements feebly and unsteadily but is able to offer resistance proportionate to the full force of the counter movement made by the examiner In *myotonia* the ability to relax a contraction is impaired (*grasp* or *closure of the eyes*) This delay in relaxation of the grasp is also present in *disorders of the opposite frontal lobe and rostrum of the corpus callosum* It is then associated with a grasping movement when the part of the palm between the thumb and the first finger is stroked (*grasp reflex*) sometimes with automatic wandering movements of the hand (forced groping)

The excitability of muscles should be noted In *congenital myotonia, acquired myotonia* and *dystrophia myotonica* percussion elicits a sustained local contraction lasting for more than a minute Contraction of muscles as a result of occlusion of the circulation is limited to *tetany* (Trousseau s sign) *Fatigue* increases all muscular weaknesses but only in *myasthenia gravis* does actual paralysis follow use of the muscles (See page 902 for discussion of myasthena gravis)

Postural Tone Any undue resistance of the muscles to passive manipulation should be noted and a record made of the muscles or muscle groups affected The resistance accompanying *pyramidal system defect* usually has a 'clasp knife" character The resistance is greatest just as passive stretch begins, and releases suddenly as the stretch is persisted in If the speed of the passive movements is increased, the resistance will also increase

Coördination Action or intention tremors are best elicited and studied by the finger nose finger and heel to knee tests with the eyes closed Lack of cerebellar control produces such decomposition of movement Rapid alternating movements such as patting the knee and rapidly pronating and supinating the hand are impaired It may be observed that the patient walks on a wide base and takes long steps There may be rhythmical tremors at right angles to the line of movement

Spasticity This is best estimated by passive manipulation while the patient relaxes as much as possible Slight degrees of spasticity are best determined by shaking a limb sudden passive lifting of one thigh and observation of the sagging of the leg When otherwise difficult to detect, spasticity may be disclosed by having the patient run or walk when the slow flexion of the hip joints will be observed

Rigidity The rigidity of extrapyramidal disease is characterized by the more constant resistance which it offers throughout the manipulation of the joints It is seen in both flexion and extension *Cogwheel rigidity* is found with extrapyramidal tremor and is best felt by very gentle manipulation of the wrist Confirmation of the presence of extrapyramidal rigidity is seen in the ability of the patient to maintain awkward postures of the body without discomfort by the infrequency of winking and of changes in facial expression and the absence of the natural swing of the arms in walking

Hysteria should be suspected when the rigidity shows inconsistencies and variations from moment to moment Hysteria or some local painful lesion should be suggested if there is pain or rigidity on manipulation When the limitation of passive movement is firm and fixed the muscle is either shortened (contracture) or the condition of the joint merits special inquiry

Hypotonia This is best estimated by watching the movements of the joints when they are shaken or suddenly displaced An other useful test is the *rebound phenomenon* of *Gordon Holmes* When the patient pulls hard with semi flexed elbow against the examiner s hand which is then suddenly released the hypotonic limb will show a lack of braking action

rhythm is characteristic and most pronounced in the smaller parts i e , the thumb and fingers (pill rolling ' movements) It ceases tem porarily upon movement In *multiple sclerosis* tremor is intensified by action intention or attention The tremor seen in *exophthalmic goiter* is fine and rapid and seen particularly in the outstretched hands The *alcoholic* patient may show a tremor of the lips and tongue In

TABLE LIII

Muscle	Action	Nerve Supply	Segment of Cord
Deep muscles of neck	Flexion and extension	Cervical nerves	C1 to C4
Sternomastoid	Rotation of head	Spinal accessory	Medulla & C1–C3
Trapezius	Raising shoulder also arm above horizontal level	Spinal accessory	Medulla & C1–C4
Diaphragm	Inspiration	Phrenic	C3–C5
Pectoralis	Adduction of arm	Thoracic	C5–C8
Deltoid	Abduction protraction and retraction of arm	Axillary (circumflex)	C5
Serratus anterior	Fixation of scapula	Long thoracic	C5–C7
Biceps	Flexion and supination of forearm	Musculocutaneous	C5–C6
Brachioradialis	Flexion of forearm	Radial	C6
Triceps	Extension of forearm	Radial	C6–C7
Extensors of wrist and fingers		Radial (also ulnar)	C6–C7 (C8?)
Flexors of wrist and fingers		Median and ulnar	C7–D1
Abdominal	Flexion of body	Intercostals	D6–D12
Iliopsoas	Flexion of thigh	Femoral	L1–L3
Gluteus maximus	Extension of thigh	Inf gluteal	L5–S1
Quadriceps	Extension of leg	Femoral	L2–L4
Adductors	Adduction of thigh	Obturator	L2–L4
Biceps semimembranosus and semitendinosus	Flexion of leg	Sciatic	L5–S2
Soleus and gastrocnemius	Plantar flexion of foot	Tibial	L5–S?
Peroneal group	Dorsal flexion of foot	Common peroneal	L5–S1
Perinei and sphincters	Control of sphincters and sex act	Pudendal	S3–S5

Flaccid Paralysis If flaccid paralysis is present does it correspond to the distribution of segmental nerve roots? Does it have an upper level corresponding to the innervation of one nerve root? Does it correspond to the dis tribution of a peripheral nerve or a group of nerves? A table of the radicular and peripheral nerve supplies and actions of the muscles fol lows and may prove useful in the examination

Spastic Paralysis Is spasticity or spastic paralysis present? What is its upper level? What is the highest segment affected?

Involuntary Movements *Tremors* Note their *location rate amplitude* and *rhythm*

The tremor of *paralysis agitans* is seen best when the patient is at rest Its steady slow

addition *Quinquaud s finger crepitation* may be elicited by having the patient extend his fingers at the inter phalangeal joints and press them at right angles to the palm of the examiner s hand which is held in a vertical position After a few seconds a series of slight shocks can be felt *Senile tremor* is not unlike the tremor of paralysis agitans but it appears much later in life Furthermore it is bilateral and is not accompanied by the rigidity seen in Parkin son s disease A tremor termed *spasmus nutans* has been described in the literature It is said to occur in rachitic children especially during the seond six months of life It is a peculiar involuntary rotatory or nodding tremor of the head It usually comes on in the

winter time, and in addition to the head tremor there is a fine rapid nystagmus which may be more marked in one eye than in the other It is not associated with any mental defect *Hysterical tremor* may have a rhythm not unlike that of paralysis agitans but its important features are an increase in amplitude with attempted movement or on command to cease the movement, and the spread of the tremor to other joints when the affected part is grasped firmly

Athetoses These are slow irregular purposeless movements They may be unilateral or bilateral They are observed mainly in the fingers and toes and are practically constant and not infrequently accompanied by associated movements in other parts of the body, such as grimacing and spasms of the neck with abduction and extension of the lower limbs *Pseudo athetosis* is seen in *tabes* and *combined sclerosis* (in those whose sense of position is impaired) It is seen in the fingers and is elicited by having the patient close his eyes and stretch out his hands

Tics Tics are involuntary convulsive movements They are rapid and stereotyped They are repeated periodically in exactly the same way each time The movement fluctuates in frequency with varying degrees of emotional tension This is contrasted with the fixed regular more purely involuntary spasm seen in organic disease (Chorea)

Choreic Movements These are rapid, purposeless, irregular spontaneous and arrhythmic They are seen best in the outstretched limbs as sudden small flexions of the wrist finger or elbow The movements are always unpredictable They may be limited to one side or to a limb, in which case the term *hemichorea* is applied to them They may be confined to the tongue eyeballs or diaphragm The gait is characteristic The patient cannot walk slowly and his gait may be dancing, clownish or bizarre In severe degrees of chorea the movements become more active when the patient seeks rest and may be sufficient to throw him out of bed

Myoclonus Myoclonus is a sudden irregular or regular contraction or shock like jerk of a muscle but which, as a rule, causes no effective movement Such twitchings are often lightning like as if produced by an electric shock

Hiccup is a spasmodic myoclonus of the diaphragm

Spasms These are slow, sometimes prolonged pattern movements which may occur anywhere in the body They are not so rapid or clonic as tics They may persist during sleep They are frequently conversion symptoms of hysteria They often occur in the face and in the eyelids (blepharospasm) While they may often be due to psychogenic disorders, they are frequently the sequelae of *epidemic encephalitis*

THE USE OF REFLEXES AS DIAGNOSTIC SIGNS

The reflexes serve as sensitive indicators of the state of the nervous center, or of the afferent or efferent pathway In health the deep, superficial, and tonic reflexes are equal on the two sides of the body It must be remembered that past disease or some present disability not necessarily of neurological significance may alter them For example, the knee jerks may be lost as a result of a previous *diphtheria* or the abdominal reflexes may be absent owing to laxity of the abdominal wall as may follow repeated pregnancies It is often important in clinical diagnosis to establish the level at which the disease process begins and ends It is of value to know the condition of the *tendon reflexes* in determining this level, particularly if the state of the reflex arcs at successive levels of the cord is tested If the *tendon reflexes* of the arms are altered, this will place the lesion higher than if those of the legs alone are modified The *superficial reflexes* are also valuable as an aid in neurological diagnosis The *abdominal* and *cremasteric reflexes* are abolished by any disease process destroying or depressing the reflex arc from the 10th thoracic to the 2nd lumbar segments These reflexes are reduced or lost in disease of the *pyramidal tract*

The *superficial reflexes* are obtained by gently stroking or scratching the skin with a blunt object The *deep reflexes* are obtained by percussion of the tendon of a muscle with a rubber (preferably) reflex hammer There are several other interesting reflexes but they are of little use as sensitive physical signs,



A Knee jerk in the recumbent patient



B Knee jerk in the ambulatory patient



C Ankle jerk in the ambulatory patient



D Ankle jerk in the recumbent patient



E Triceps jerk Percussion of the triceps tendon causes contraction of the muscle with extension of the elbow



F Biceps jerk A tap on the biceps tendon causes contraction of the biceps and flexion of the forearm

Fig 167 Reflexes and Signs of Diagnostic Value

since they appear only after severe spastic paralysis with increased tendon reflexes have already made it obvious that the conducting pathways of the spinal cord have been damaged The *Chaddock* and *Gordon* signs which are variants of the Babinski sign occur only, when as a result of increasing damage, the reflexogenous area has spread widely from its initial focus on the outer border of the foot, they are, for this reason, less sensitive than the Babinski response

In all suspected *conus or cauda equina lesions* and in *cases of sphincteric disturbance* the *tendon reflexes*, the *abdominal reflexes*, and the plantar responses as well as the anal and bulbocavernous reflexes should be examined The standard deep reflexes which should be tested are the *biceps triceps radial periosteal* and the *knee* and *ankle jerks* The biceps jerk is elicited by pressing on the biceps tendon with the left thumb and percussing the thumb, and the triceps jerk by percussing the tendon just above the olecranon Percussion of the head of the radius causes a slight contraction of the muscles of the forearm which may spread to the biceps *Ordinarily these are all sluggish responses* The ankle jerk may be extremely sluggish in normal individuals It is best tested by causing the patient to kneel on a chair When the knee and ankle jerks are difficult to obtain reinforcement should be tried This is accomplished by asking the patient to squeeze his hands together tightly, or to count backward from 20 to 1 slowly For a satisfactory elicitation of the tendon reflexes adequate muscular relaxation is essential A certain degree of passive tension on the muscle is also necessary and, in the case of the radial and ankle jerks the examiner may have to vary the tension on the muscle by manipulating the joint before he can be certain that the jerk is absent When the patient is in the recumbent position the best position for eliciting the ankle jerk is with the thigh rotated outwards the knee semi flexed and the ankle a little inverted The *plantar response* can be tested with the foot in the same position although if there is any difficulty the leg should be extended fully In evoking the *triceps jerk* it is important to disregard the small contraction of those muscles directly percussed with the hammer for as a rule they will in any case contract to direct stimulation It is well to remember that in a small percentage of otherwise normal people tendon reflexes are absent A slight *finger jerk* is present normally and is of value only when its briskness on one side is such as to confirm the suspicion of a one sided increase in the arm jerk Also, a slight *jaw jerk* is sometimes present normally and only when there is a very brisk response may it be taken as evidence of an upper motor neurone lesion of the cranial nerves

The abdominal reflexes are valuable chiefly when there is a difference between the two sides or when they are lost below a segmental level which coincides with other evidence of a disturbance at that level The upper abdominal reflexes are the most sensitive and are obtained by light stroking from the lower ribs over the epigastrium Abdominal distension a full bladder, and menstruation also abolish the reflexes temporarily, so that bilateral loss is significant only as a confirmation of other evidence of an upper motor neurone lesion The abdominal reflexes may be absent in elderly people in multiparae and in the obese Any healed lateral abdominal incision may cause their absence owing to the severance of the nerves They may disappear completely in acute peritoneal inflammation

Significance of the Deep Reflexes Deep reflexes are abolished or diminished by any injury to either the sensory or the motor limb of the reflex arc they are increased by injury to the pyramidal system In certain conditions however, namely syringomyelia and amyotrophic lateral sclerosis atrophy of the anterior horn cells may go on concurrently with injury to the tracts controlling them, and decrease and increase of reflex action may then alternate In widespread pyramidal tract injury as is seen in complete transverse lesions of the cord or extensive damage to the motor cortex reflex activity may be destroyed for a longer or shorter interval

Other Reflexes The plantar response or *Babinski reflex* has been called the most important sign in neurology The response is not a simple reflex but is the consequence of two probably three reflex effects the balance of which is disturbed by damage to motor centers in the brain or their pathways in the

spinal cord The normal response is a slow deliberate plantar flexion of the great toe and for clinical purposes movement of the metatarso phalangeal joint alone should be observed The most suitable stimulus is a blunt object such as a Yale key for painful stimulation induces a voluntary movement which may confuse the observation stimulation of proprioceptors which are not so reliable in their responses is also avoided The site of stimulation should be the outer border of the sole of the foot for the abnormal reflex response can be evoked from this region at a time when that from the inner border is still flexor the receptive area spreads later to the rest of the sole The stimulating stroke should be deliberate from the heel to the ball of the great toe The abnormal reflex is a dorsi flexion at the metarso phalangeal joint and is often brisk Attempts to decide a doubtful response on the basis of the results of other tests such as the *Oppenheim Gordon*, and *Rossolimo* are not advised The plantar response may be absent owing to an interference with its reflex arc

If the response is sluggish or indefinite it may sometimes be clarified by bending the knees slightly In a cold room the feet may have to be warmed to a comfortable temperature The only other foot sign of real importance is the *Oppenheim reflex* It is elicited by stroking the shin with the knuckles or with the handle of the percussion hammer sufficiently hard to cause some pain The response is similar to that of the Babinski test and is occasionally positive when the Babinski is not though on the whole it is less sensitive The nearest approach to the Babinski type of reflex in the upper extremity is the *Hoffmann sign* this is evoked by snapping the nail of the middle finger of the patient with his palm held downward and his fingers limp The abnormal response is an abduction of thumb and forefinger usually however there is no response and occasionally a twitch of the thumb occurs in a normal person

Ankle clonus is occasionally present as a result of old spinal cord damage In progressive lesions it appears later than other signs and is only confirmatory of an exaggeration of ankle jerks It is important to have the ankle relaxed as much as possible with the knee semi flexed and passive dorsi flexion made suddenly but not too forcibly It should be remembered that *false ankle clonus* appears in nervous people with tense muscles and brisk jerks and it should be suspected if the gait is not spastic

The *superficial anal* reflex is a contraction of the levator ani and associated perineal muscles when a pin is drawn along the sacral skin on either side of the anus It is absent following damage to the 3rd or 4th sacral segments or their nerve roots

To conclude the *only absolute reflex sign is the plantar response Briskness or sluggishness of tendon jerks or abdominal reflexes is only significant in relation to other evidence, or when one sided*

Spinal Shock When damage to conducting pathways is sudden and severe all reflex activity below the lesion may be abolished for some days The tendon jerks after a time return and gradually become hyperactive and the plantar response progressively more abnormal In complete spinal transsection a weak flexor movement of the great toe may be found in the first week This is a small reflex from the sacral segments and is soon overcome by the more intense dorsiflexion which is part of the withdrawal reflex (the true Babinski phenomenon)

Reflex Formulae (After Monrad Krohn) (3)

1 *Pyramidal Lesion*
   a Positive Babinski sign (extensor plantar reflex)
   b Diminished or absent abdominal reflexes
   c Increased tendon and periosteal reflexes
   d Pathological shortening reflex—i e dorsiflexion at the ankle joint elicited, by pinching the dorsal aspect of the foot or ankle
2 *Peripheral Lesion* Diminution or loss of all reflexes
3 *Hysterical Lesion*
   a Plantar reflex normal
   b As a rule brisk abdominal reflexes (umbilicus chases the pin) often a difference between the two sides with corresponding sensory difference
   c Brisk tendon and periosteal reflexes
   d No pathological shortening reflex

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A Testing for epicritic sensation with a wisp of cotton



B Testing for protopathic sensibility using a pin stuck through a tongue depressor



C Testing for deep sensibility A pencil or blunt object is used The use of the blunt end of a pin is not to be recommended



D Appreciation of temperature sense is tested by applying test tubes of hot and cold water to the skin



E Examination of vibratory sense with a tuning fork In this instance the vibrating fork is placed in contact with the medial malleolus

FIG 168 Examination of the Sensory System

4 *In Certain Cases of Extrapyramidal Motor Lesions (Paralysis Agitans and Chorea)*
 a Normal plantar reflex
 b Increased abdominal reflexes
 c Retarded or diminished tendon reflexes
 d No pathological shortening reflex

Pathological States in Which the Deep Reflexes Are Diminished or Increased (after Spurling) (4)

The Deep Reflexes Are Diminished

1 In diseases of the joints (acute and chronic), muscles (myopathies) and tendons (traumatic) the deep reflexes in that region may be diminished or absent

2 After prolonged administration of sedative drugs (bromide phenobarbital etc) the deep reflexes may be greatly diminished

3 In lesions of the peripheral nerves, such as toxic neuritis from alcohol or lead inflammatory lesions like sciatic neuritis and traumatic injuries to the nerves, the regional deep reflexes are diminished or absent

4 In lesions of the dorsal columns of the cord such as tabes and combined sclerosis, the deep reflexes are diminished or absent due to the break on the afferent side of the reflex arc

5 In lesions of the anterior horn cells such as poliomyelitis, syringomyelia and primary muscular atrophy, the deep reflexes are abolished due to the break on the efferent side of the reflex arc

6 In acute injuries to the cord involving the pyramidal tracts these reflexes are, as a rule abolished for a time which varies from a few weeks to months Usually the state of diminished reflex activity is followed by a great exaggeration of the deep reflexes

The Deep Reflexes Are Increased

1 In the neuroses and psychoneuroses the tendon and periostal reflexes as a rule are exaggerated This hyperactivity is not accompanied by other signs of disease of the pyramidal tracts such as abolition of the superficial reflexes and a positive Babinski reaction

2 In a lesion of any sort involving the corticospinal pathways, whether it is in the motor cortex internal capsule pons medulla or spinal cord, there is an exaggeration of the deep reflexes below the level of the lesion on the side to which these fibers are distributed In amyotrophic lateral sclerosis an unusual situation exists In addition to anterior horn degeneration, as in primary muscular atrophy, there is degeneration of the corticospinal system For this reason hyperactive reflexes are often observed even in the presence of muscular atrophy The only exception to this rule is in the case of acute injuries to this system, when the reflexes may be temporarily abolished

3 In tetanus and strychnine poisoning, the deep reflexes may be temporarily abolished

EXAMINATION OF THE SENSORY SYSTEM

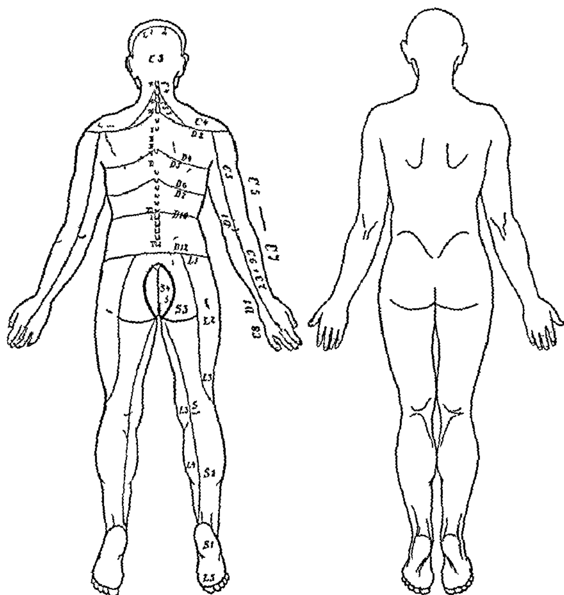
It is unnecessary in every patient to test each small part of the skin surface with all modalities of sensation However, it is advisable as a routine to test each of the four extremities for changes in *sensation* to *touch and pin prick* and for the *sense of position* in the joints of the fingers and toes, for one will then sometimes pick up a change in one or other form of sensation of which the patient is not aware

Indications for a Further More Complete Study

1 Any complaint on admission or at the first interview of *numbness, pins and needles' tingling coldness* or *pain* These should have careful tests for touch pain heat and cold position sense and vibration sense in the part concerned
2 The finding of localized atrophy or weakness
3 The presence of ataxia should always lead to careful estimation of position and vibration sense
4 Trophic changes especially painless ulcers blisters and joint affections should lead to careful testing for loss of the sense of pain
5 When a cerebral lesion is suspected discrimination sensation (position sense, two point discrimination) should be estimated on the two sides

Examination for Tactile Sensation

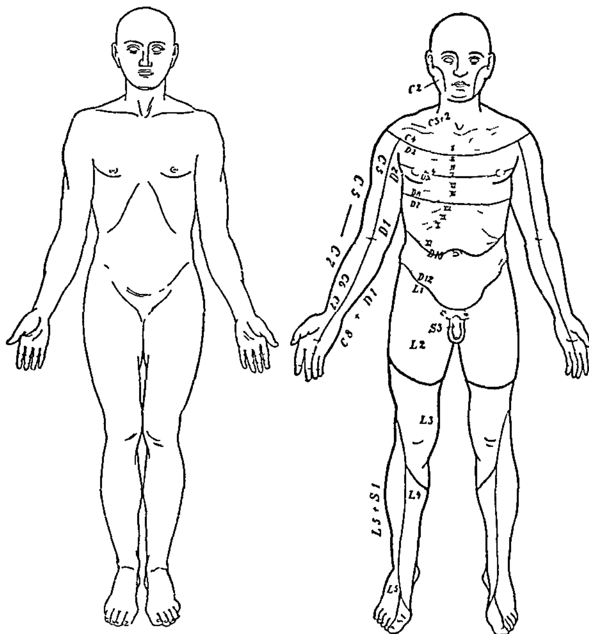
Sense of touch is best tested with a small wisp of cotton wool, twisted so as to leave



in sensation when a pin point is lightly dragged over the skin When an area of sensory loss is charted it may be considered whether it is consistent with an area of segmental skin innervation (see chart on page 868–9) or with the pattern of any peripheral nerve or nerve group If there is a loss or diminution of sensation below a particular level one should determine whether the two sides are equally involved The ordinary distribution of the sensory changes may be altered owing to the longest fibers being more severely affected this is seen in some kinds of neuritis It is easier to map out the change in sensation to pin prick and then re examine for other sensations in order to discover whether all forms of sensation are lost to the same degree or are affected differently (dissociated sensory loss)

If an area is actually anesthetic it will endure a series of rapid blows with the pin in a single spot which is far more noxious than a single deep prick

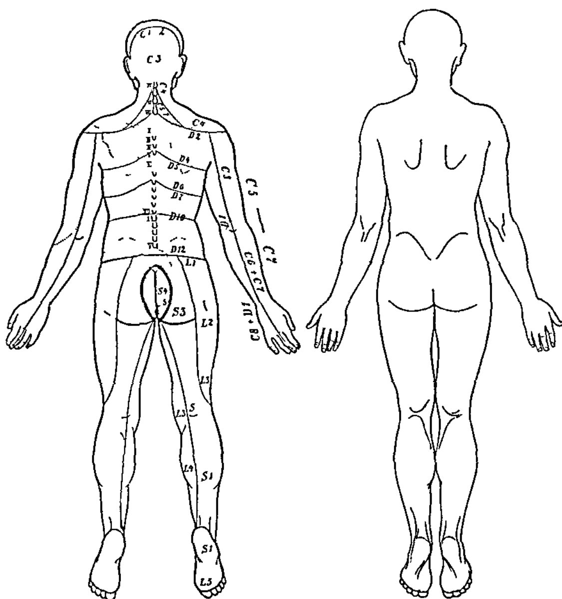
Inconsistency in replying should always lead to a suspicion of *hysteria* and cause one to devise other means of testing sensation (i e, is there astereognosis or incoordination



only a few fibers at its tip Care must be taken to avoid hairs in critical testing for the hair follicle is a coarse receptor Allowance must be made for the thicker skin on the palm and sole For stronger stimulation light strokes may be employed It is best to have the patient count each time he feels the touch otherwise he may neglect to inform you

Examination for Pain Sense

The *sense of pain* is tested by pin prick which should be applied evenly and not too rapidly A speed of about one a second is best If there is an area that does not give a response, or in which sensation is blunted, it is well to define it by testing in all directions radiating from its center marking with a skin pencil or other marker the points where it merges into normally sensitive skin It is important to realize that in many kinds of sensory loss the border is not sharp but is a zone of graduated impairment Therefore deeper, heavier pin pricks will show a smaller area of loss than will a series of light pin pricks Very slight changes can be outlined in a cooperative patient by getting him to indicate the changes



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If an area is actually anesthetic, it will endure a series of rapid blows with the pin in a single spot, which is far more noxious than a single deep prick.

Inconsistency in replying should always lead to a suspicion of *hysteria* and cause one to devise other means of testing sensation (i.e. is there astereognosis or incoordination

commensurate with the supposed sensory loss, or is the sensory loss changed by strong counter suggestion) It is very easy for sensory loss to be suggested to an anxious patient by the very fact that it is being tested This usually begins by the patient making too much of some small difference If he complains that there is a difference between one side and the other, one should try to decide how much difference there is by using different intensities of pin prick It is usually possible to break through the early stages of suggested analgesia by repeated pin pricks In special forms of sensory loss (syringomyelia) acute touch sensation is retained which enables the patient to say it s sharp " though he may not feel pain When this is suspected, he should be asked to indicate whether the prick causes pain Observing how much he winces when equivalent pricks are applied to different areas is a more objective means of testing

Tracy Putnam has said that the sensory examination is only as good as the *entente* between the subject and the examiner Fatigue or ill humor on the part of either minimizes the value of the examination One should avoid suggesting the boundary of an area of hypoesthesia to the patient The common hypoanalgesia confined to one side stopping exactly at the midline of both face and body and occasionally accompanied by dimness of vision and deafness on the same side is the *mildest form of hysteria* See Figure 168

In lesions of the spinothalamic pathway and sometimes in lesions of the cerebral cortex *raised threshold for pain with o er reaction* is a common occurrence Single pin pricks at long intervals are then appreciated or felt as dulled More rapidly repeated pricking is suddenly felt as something intensely painful more painful than on the normal side Then abnormally prolonged tingling may be experienced after a single severe prick

Examination of Temperature Sense

It is rarely essential to determine the sensitivity to heat and cold except when the question of *syringomyelia* arises with its characteristic dissociation of sensation When the test is desired two test tubes filled with hot and cold water are used The area of sensory loss to heat is usually larger than that to cold The two tubes are pressed against the skin at random and the patient is asked to indicate the temperature changes When a loss is detected, the tube should be moved along the skin until a change occurs The areas of loss should be charted with oblique lines, directed one way for heat, and another way for cold The author has found the use of rubber anatomical outline stamps invaluable for this work Many of those shown on the history and physical examination forms in this volume are furnished by the Barton Mfg Co 150 Nassau Street, New York City

Examination of Joint and Position Sense

In testing for sense of position it is necessary to hold both segments of the joint firmly in order to prevent any difference in cutaneous contact from indicating the movement at the joint Each movement should be varied in degree for inability to recognize large movements occurs only when a severe loss in the sense of position has occurred In spinal diseases the loss of position sense is usually maximal in the toes and fingers but in some kinds of polyneuritis it may affect the proximal joints and not the distal thus causing an ataxia of gait with retention of position sense in the great toe To demonstrate this, the patient should close his eyes and then manipulate his leg to some extreme angle he is then asked to point to where he thinks his great toe is

Examination of Vibratory Sense

Testing for vibration sense with a tuning fork of deep pitch is important in the study of mild degrees of damage to the spinal cord It is best felt over any hard resistance and thus, usually over bony prominences such as the styloid process of the radius and ulna the olecranon clavicle ilium, tibia and lateral and medial malleoli The tuning fork with a low rate of vibration (128) should be used, and the heavier the better For exact work, a fork with an attachment indicating a standard amplitude of vibration is used and the time measured during which the sensation is felt For ordinary clinical purposes it is sufficient to record loss or diminution of the sensation which should be a distinct vibratory thrill This should not be confused with a sense of discomfort or touch caused by pressure

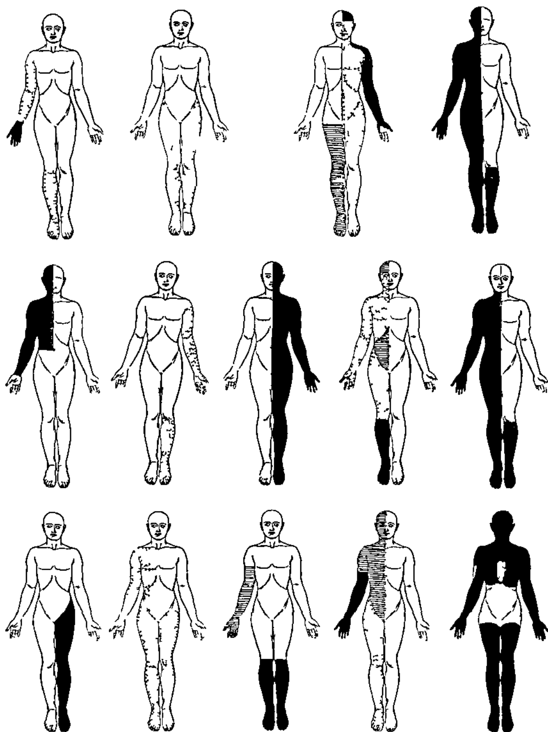


FIG 169 Types of Hysterical Anesthesia
The stippled areas indicates slight sensory loss the striped areas more severe sensory impairment and black areas represent total loss of sensation

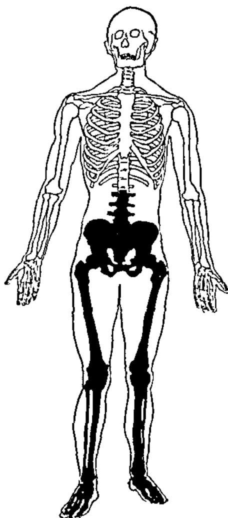


FIG 170 Loss of Vibration Sense in Tabes

of the fork upon the skin Loss of vibration sense is sometimes more severe than loss of position sense (in *combined system disease*) and sometimes just the reverse (*multiple sclerosis*) but both types of sensation are usually affected together in some degree except in cortical lesions Vibration sense is diminished in the aged and is impaired by adiposity

Examination of Point Discrimination

Damage to the sensory mechanism above the level of the thalamus affects the ability to make certain sensory discriminations The most easily tested is the ability to appreciate joint movement Position sense may be lost and ataxia occur without loss of vibration sense from parietal cortical lesions When this occurs there should also be some loss of the ability to discriminate two points from one A *compass with blunt tips* is used for this examination and the distance apart adjusted according to the normal threshold for the part tested These normal distances are

Finger tips	3 to 4 mm
Back of hand	30 mm
Palm of hand	8 mm
Forearm	40 mm
Arm and thigh	80 mm
Dorsum of foot	40 mm
Toes	12 mm

One should begin on the normal side and be satisfied that the patient can discriminate between *a light pressure for two or three seconds of one point and two points* The abnormal side should then be tested The patient is told to say 'one' or 'two according to whether he feels one or two points The results are recorded in two columns (one point and two point) indicating a correct answer by a stroke and an incorrect one by a cross

The same loss of sensation can be shown more easily, but not so accurately by writing numbers with a blunt object on the patient s skin while his eyes are closed and getting him to indicate what the number was With this type of sensory loss there is also difficulty in the *localization* of the points touched They should be charted by marking the point with a cross on an anatomical outline of the part, and connecting this by a line to an arrow head showing where the patient thought he was touched

Astereognosis

True astereognosis is a defect at a higher level, a lack of perception of the size weight and shape of an object held in the hand, the primary sensations being intact It is associated with lesions lying behind the sensory cortex proper In actuality there is usually some impairment of tactile discrimination present Lack of recognition of form however may be present in cord (dorsal column) and medullary lesions and is then dependent upon the more elementary disorder of position and tactile senses

Significance of Sensory Changes

If all the abnormal findings have been sensory in nature it is well to review them with an

eye to the possibility that they have been suggested by examination, and are not the result of disease. Beware of reliance on a sensory change which is unaccompanied by any complaint such as numbness, parathesiae or ataxia. In doubtful cases confirmation of sensory disturbances can be obtained from sweating tests for in peripheral nerve lesions and also many types of central lesion the sympathetic supply suffers disorder over a similar area. (See page 881 for technique of sweating tests.)

The areas of loss of sensation following *peripheral nerve injury* correspond to the distribution of the nerve, pain is more affected than touch and there may be hyperesthesia as well. In *polyneuritis* hypesthesia of a 'glove and stocking' distribution is the rule fading off toward the trunk. These areas of sensory loss are easily confused with the hysterical anesthesias which are also of the 'glove and stocking' type. In *hysteria*, the loss of feeling of hysterical origin is complete, ending abruptly at a joint and being accompanied by a contracture, weakness or tremor. A myelopathy resulting from deficiency diseases such as *pernicious anemia* or *pellagra* is suggested by the coexistence of hypesthesia of the hands and feet with evidence of disease of the spinal cord (increased reflexes and Babinski sign). The loss of sensation resulting from a local lesion in the cord can usually be interpreted by consulting a standard diagram of the tracts.

PARALYSIS

The state of tonicity of paralyzed muscles is a fairly accurate guide as to whether the lesion involves the upper or lower motor neurone. The neurones responsible for voluntary motor action run in two relays. The first portion of the voluntary motor tract from the cerebral motor cortex to the junction with the motor cells in the anterior horn of the spinal cord is called the *upper motor neurone*. The portion composed of the anterior horn cells and the nerve fibers to the muscle is called the *lower motor neurone*. See figure 171.

There are striking contrasts between the physical signs of upper and lower motor neurone affections. These differences are summarized in table LIV.

TABLE LIV

Upper Motor Neurone Lesion	Lower Motor Neurone Lesion
Paralysis affects movements rather than muscles	Individual muscles may be affected
No muscular atrophy except from disuse	Pronounced wasting of atrophied muscle
May have associated movements on attempted voluntary movement	No associated movements
Muscles hypertonic	Muscles flaccid and hypotonic
No trophic skin changes	Skin cold, blue, shiny—may ulcerate
Deep reflexes present and usually increased in the paralyzed limbs	Deep reflexes diminished and often absent of the paralyzed muscles
Superficial reflexes diminished or absent	Unaltered superficial reflexes
If foot affected the plantar reflex is extensor in type	Plantar flexion if present normal
Electric reactions normal	Reaction of degeneration

THE EXAMINATION OF THE CRANIAL NERVES

A thorough systematic examination of the cranial nerves should be a routine procedure in every neurological case. Primary lesions of the cranial nerves, their nuclei or controlling centers may thus be found as well as secondary involvement through disease of the meninges or the brain.

I. *The Olfactory Nerve*

Partial or complete anosmia may be due to rhinitis, therefore examination of the first cranial nerve is often of questionable value. Its anatomical position however renders it liable to damage from (1) tumors in the frontal lobe or (2) fractures of the floor of the anterior cranial fossa. Other causes of anosmia may be (1) cerebellar tumor, (2) atrophy of the olfactory nerve in tabes and (3) hysteria. In testing, one nostril should be closed while wool soaked in *oil of cloves, peppermint, lemon, camphor, vanilla, menthol* or *coffee* is held under the other nostril. Volatile or pungent odors should not be used for this test since they stimulate the sensory endings of the 5th nerve. *Perversions of smell are frequently present in abscesses or tumors involving the inferior or*

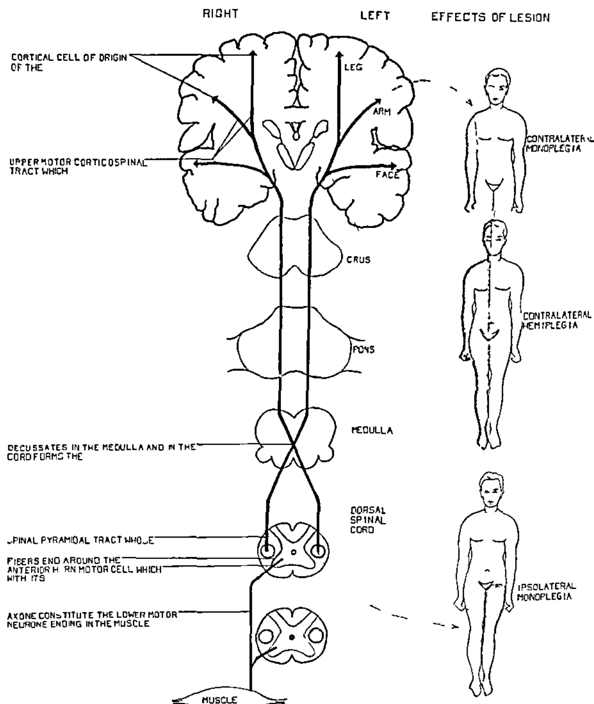


Fig 171 Diagram to show the extent of the upper and lower motor neurones and the effects of a lesion in different parts of the motor system Only the common positions for a lesion have been illustrated

deeper portions of the temporal lobe These uncinate fits may occur as an aura in epilepsy or constitute the entire episode

II Optic Nerve

This is the most important of the cranial nerves Visual acuity is tested by the use of Snellen charts The visual acuity is recorded as

$$U O D = \frac{20}{\text{size read}}$$

$$U O S = \frac{20}{\text{size read}}$$

$$\text{Normal vision is } \frac{20}{20}$$

Uncorrected and corrected if glasses are worn

If distant vision is good but there is impairment of ability to read the subject should be tested with *Jaeger type* test cards recording the smallest type read by the patient at visual reading distance

Visual Fields Gross defects in the visual fields can be easily detected by the confrontation test The patient and examiner sit facing each other with their chairs about two feet apart The patient is directed to look at one of the examiner's eyes (right eye if the patient s left is being tested and vice versa) while the eye not being tested is covered The examiner then holds up both his hands and moves his fingers and asks the patient to indicate the side on which he sees the fingers moving His ability to detect small movements in all quadrants of each field should be tested Movement on both sides simultaneously should next be tried because lesions of the hemisphere outside the visual cortex sometimes cause failure to appreciate movement in one field when a moving object is presented concurrently to the field of the opposite side (attention hemianopia) whereas if the movement is confined to the affected side it is appreciated

For an accurate record the *arc or screen perimeter* is of great value In charting fields on the perimeter the white objects subtending 1 and ½° are standard They should be moved slowly In the presence of a refractive error only 1° is reliable The size of object used should be stated on the record The smaller the object the more sensitive the test Normally the visual field is larger for blue than for red and larger for red than for green In *hysteria*, there may be a contraction of the visual field it is larger for red than for blue A spiral visual field is a symptom of *fatigue* Scotomata must be mapped by the stereoscopic method for accuracy

The effect of lesions in the different portions of the visual pathway are described on page 876 figure 172

Ophthalmoscopic Examination This procedure should be included in every examination and especially when symptoms referable to the head are prominent The use of mydriatics to dilate the pupil is unnecessary Placing the patient in a dark room will usually dilate the pupil When a dark room is not available, pinching the patient s neck, which will elicit the cilio-spinal reflex usually produces a prompt homo-lateral dilatation of the pupil sufficient to permit a cursory examination of the fundus The presence of optic atrophy or a choked disk should be sought

Points to Observe in the Ophthalmoscopic Examination

1 Color of disk	Normally pale pink White in optic atrophy Red or greyish red in *papilledema and in primary optic atrophy*
2 Border of disk	Normally well defined and distinct Black choroidal crescent at temporal margin Blurred in *papilledema* and *secondary optic atrophy*
3 Swelling of disk	The swelling should be measured in diopters Plus lenses are added until the retina is out of focus the value is then reduced until the first part of the disk is in focus The same is done for some small vessel near the macula The difference in lens value equals the swelling in diopters 3 diopters equals 1 mm of swelling
4 Retinal vessel	Are vessels constricted or distended? Do the arteries indent the veins where they cross? Any pulsation of vessels? Any hemorrhages? Any exudate on the retina?
5 Opacities of lens.	

Fig 172 The optic pathway showing how lesions at various points will be exhibited in the fields of vision upon perimetric examination The red areas in the small perimetric fields on the right correspond to the lesions marked on the left hand figure as follows

A Total blindness in the left eye from inflammation tumor trauma or vascular occlusion

B Bitemporal hemianopsia from inflammation chiasmal neuritis syphilitic meningitis aneurysm pituitary tumor and fracture of the base

C Nasal hemianopsia in the left eye

D Right homonymous hemianopsia Common causes are tumor meningitis or aneurysm

E and F Right upper and lower quadrantic homonymous hemianopsias Common causes are hemorrhage cerebral softening and tumor

G Right homonymous hemianopsia with preservation of central vision (Arterial obstruction—cortical softenings angiospasm in migraine hemorrhage abscess tumor trauma)

INT CAR—Internal carotid artery

PIT—Pituitary body

POST CEREB—Posterior cerebral artery

EXT G B—External geniculate bodies

During the early stages of *papilledema* in which the vision is beginning to be impaired a concentric constriction of the fields and an enlargement of the blind spot is present Later scotomata appear and the constriction of vision continues In *optic atrophy* the disks are white or bluish white the cupping is exaggerated and the lamina cribrosa is plainly visible When atrophy is far advanced the small vessels disappear over the disk which appears like a full moon in a cloudless sky

III—IV—VI Nerves

These nerves comprise a functional unit in that they are all concerned with movements of the eye Injury to the 3rd nerve causes dilatation of the pupil and a limitation of the bulb except for lateral rotation Injury to the 4th nerve impairs the ability to look down and in Injury to the 6th nerve makes complete abduction impossible The methods of testing the movements of the eye and the pupillary reactions are obvious The essential component of *nystagmus* is the slow phase Nystagmus is considered to exist when there are more than three jerks on extreme lateral or vertical fixation It occurs in organic diseases involving the midbrain pons cerebrum vestibular pathways and the cervical cord When *diplopia* is complained of a lead to the involved muscle may be gained by asking whether the diplopia occurs on looking downward upward to the right or left

In lesions of the oculomotor nerve both light and accommodation reflexes are equally diminished or absent Neither direct nor consensual light reflexes can be elicited in the homolateral eye Isolated transient ocular paralysis is usually due to *syphilis multiple sclerosis encephalitis* or *arteriosclerosis*

Undue prominence of one or both eyes (proptosis or exopthalmos) should be looked for by standing behind the seated patient and looking down on his face from above observing the prominence of the cornea on each side in relation to the eyebrows

Horner's Syndrome Narrowing of the palpebral fissure occurs in lesions of the cervical sympathetic trunk and is manifested by the following findings on the affected side

a Narrowing of the palpebral fissure

b Enopthalmos (paralysis of the muscle of Muller)

c Miosis due to paralysis of musculus dilator pupillae

d Ipsolateral anidrosis of the face and neck

e Ipsolateral vasodilatation of the head and neck vessels

Strabismus Many cases of squint are non paralytic and are called concomitant The differences are here summarized

P lyt c St b m	*C ncom ta t St b m*
1 S dd ns t—known a e	1 G d l onset in arly ch ld hood
2 D pl p p ese t	2 No d pl pia
3 Lim t t on of ocular mo e- m t	3 N lim tat on f ocula movem ts
4 V iation of isual xis s g t ed n differ t dire t	4 V iat n th isu l a
5 V bh dn s	5 Eye m y b ambly p
6 F l e p ject	6 N f lse p ject n
7 V t g m y occur	7 No ert g

V Nerve (Trigeminal)

In testing sensation in the distribution of the 5th nerve one must have a clear mental image of the cutaneous area which it supplies (see figure 173)

The most delicate test for trigeminal sensation is to touch the cornea with a wisp of cotton Loss of corneal reflex is often an early sign of V and VII nerve affection encountered in cerebello pontine tumors A pin or small brush can be used to delimit areas of hyperesthesia The two masseter muscles on each side should be felt when the patient bites hard and whether they contract equally or are wasted should be noted Does the mandible deviate to one side (paralyzed or weak pterygoid muscles) when the patient attempts to lower the jaw against resistance? This tests the motor root of the 5th nerve If the pterygoid muscle is paralyzed the patient is unable to move the jaw to the opposite side

Destructive lesions of the 5th nerve are seen in disease involving the pons cerebellum and the cerebello-pontine angle *Acoustic neuromas* are usually associated with some sensory loss in the distribution of the 5th nerve *Trigeminal neuralgia* is one of the most frequent affections of the nervous system requiring surgical treatment (For discussion see page 903) A unilateral trigeminal palsy suggests a nuclear or an infranuclear lesion

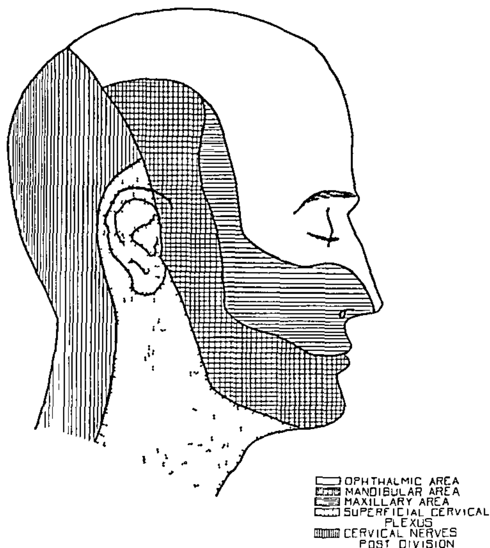


FIG 173 Diagram Showing the Superficial Sensory Distribution of the Trigeminal Nerve

since the motor nucleus of the 5th nerve receives innervation from both hemispheres Monrad Krohn however believes that in some persons the motor nucleus is innervated solely or predominately from the motor cortex of the opposite side

VII Nerve

Any one sided appearance of the patient s face should be noted while the history is being taken when he is talking as well as when at rest One should have him show his teeth shut his eyes tightly frown raise the eye brows, and smile Is the weakness more obvious in the lower facial muscles when he closes his eyes? Is there any tremor or spasm of the facial muscles? Look for perioral tremors in the course of movements of the lips They may be absent with full movement Mild degrees of weakness of the peripheral type may often be detected by the force required to lift the closed lids

In cortical or subcortical lesions involving the VII nerve alone, the muscles below the lower lid are involved In the peripheral type of facial paralysis all the facial muscles are more or less affected

Bell s Phenomenon This name is applied to a condition in which the eye remains open in spite of the patient s attempts to shut it The eyeball moves upwards and slightly out ward the cornea passing under the upper lid

Supranuclear types of facial weakness occur in lesions involving the frontal, temporal or parietal lobes of the cerebrum, in apoplexy (capsular hemorrhage) and in occlusion of the middle cerebral artery. Peripheral paralyses are seen in diseases involving the cerebellum, pons, cerebello-pontine angle and medulla or of the nerve itself from the nucleus in the pons to the peripheral distribution.

Taste is tested by placing a small amount of sugar or salt on a moistened piece of gauze and gently rubbing it on the coarser folds along the lateral border of the tongue about half way back from the tip. Each half should be tested separately, the patient being directed to protrude his tongue to the opposite side and nod when he tastes anything. The test is spoiled if he draws his tongue back into his mouth while the tests are being made. For the posterior third of the tongue only the galvanic test can be applied.

TABLE LV

Characteristics of VII Nerve Lesions (after Monrad-Krohn)

1 Lesions of the VII nerve trunk peripheral to the chorda tympani leaving the nerve	1 Paralysis of the whole corresponding side of the face including the upper portion. Reaction of degeneration (R D) present
2 Lesion central to departure of chorda tympani but peripheral to geniculate ganglion	2 Paralysis of whole corresponding side of the face as in (1). Loss of taste in anterior 2/3 of the corresponding side of the tongue. Reaction of degeneration
3 Lesion between geniculate ganglion and the pons	3 Paralysis as in (1). Some deafness. If the acoustic nerve is intact hyperacusis is present as a result of stapedius paralysis. Reaction of degeneration
4 Pontine lesion nuclear or infranuclear	4 Paralysis of whole corresponding half of the face. No disturbance of taste or hearing. Usually accompanied by abducens paralysis. Reaction of degeneration
5 Supranuclear lesion	5 Paralysis never complete and exclusively confined to the lower portion of the face, the upper portion being intact or slightly affected. Paralysis on opposite side of lesion. Reaction of degeneration absent

VIII Nerve

Cochlear Division The chief symptoms referable to this division of the 8th nerve are deafness and tinnitus. A difference in hearing between the two sides is of more diagnostic importance than aural acuity itself. A simple test is to rub the thumb and forefingers beside the ear. If the sound is heard it is seldom necessary to go further. When any deafness exists one should then determine whether the source is the middle ear, end organ, nerve or medulla.

Air and bone conduction should be compared using a C 256 tuning fork and setting it into vibration with its prongs held close to the ear (air conduction) and then with the handle on each mastoid process (bone conduction). *Normally hearing by air conduction is stronger and lasts longer than hearing by bone conduction.* In deafness due to labyrinth or cochlear disease the normal relationship is maintained but the duration of each is decreased. In middle ear disease hearing by bone conduction is stronger than air conduction. Middle ear deafness chiefly affects low tone, nerve deafness high tones. In nerve deafness the fork is heard better on the sound side. Always do an *otoscopic* examination as cerumen and inflammatory lesions of the middle ear are the most common causes of deafness and tinnitus.

Vestibular Function Vertigo and nystagmus suggest vestibular irritation either of which existing alone may be due to a central

lesion No labyrinthine test is necessary in a routine examination If the drum is intact, a comparison of the effect of syringing the ear with cold water may be made if necessary (Barany Test) When the drum is not intact the galvanic test is used These are best done by a competent otologist or neurologist An absent or decreased response to these tests indicates a destructive lesion in the labyrinth or the posterior fossa of the skull cerebrum, pons, medulla, or cerebello pontine angle The response may be exaggerated in *supratentorial tumors*

IX and X Nerve

These are usually tested together as their areas of innervation seem to overlap Movements of the palate during articulation will reveal a deflection of the uvula to the stronger side *Is the gag reflex present?* Brassiness or hoarseness of the voice should lead to inspection of the vocal cords Have the patient swallow water and note any coughing or regurgitation Also look for any irregularity of the heart pulse and respiratory functions Test the posterior third of the tongue for taste with the galvanic current

XI Nerve

The patient should be asked to turn his head to the right and left against resistance while the examiner feels the contraction of the sterno mastoid muscles One should have him shrug his shoulders against resistance and observe the contraction of the upper portion of the trapezius and any wasting or spasm of the muscle

XII Nerve

Atrophy paralysis or deviation on protrusion of the tongue is easily determined Are any wrinkles present on one side? Note the force of pressure of the tongue against the inside of the cheek In advanced bulbar paralysis the tongue cannot be protruded at all, and only for a moment in myasthenia The examiner should always look for an abnormally short frenulum linguae

Articulation is a complex function involving the coordination of the fifth seventh ninth tenth, and twelfth cranial nerves The patient should be asked to say "British Constitution,' 'Irretrievable register" or 'Hippopotamus "

ELECTRICAL EXAMINATION OF MUSCLES AND NERVES

This aid to diagnosis requires special equipment and, except in some cases can be dispensed with by one with a wide clinical experience In any condition in which conductivity is lost the *faradic* responses of both nerves and muscle are absent The faradic response is the last to return and sometimes may be absent even when voluntary muscle *contraction has reappeared The galvanic* current is valuable in that it detects finer changes Since some of the nerve fibers to a muscle may be interrupted but not all the contraction induced by a *faradic* stimulus is commonly reduced but not lost This is called a *partial reaction of degeneration* ("Partial R D) The loss of faradic excitability is called the *reaction of degeneration* and is characteristic of muscle substance deprived of its nerve supply

In *myopathy (muscular dystrophy)* the essential degeneration is of the muscle fiber *itself not of its nerve* Hence in this group of diseases the muscles atrophy with only a gradual failure in faradic response and only because there are fewer or smaller fibers to respond Those fibers which respond do so as well to faradic as to galvanic current

In *myotonia* the muscle when excited electrically shows the same sustained contraction as is elicited by percussing it or by a strong *voluntary effort* In *myasthenia gravis* the contractions induced by electricity fail progressively when they are rapidly repeated Since myasthenia most commonly affects the inaccessible ocular muscles and such a severe affection of the limb muscles is uncommon this test has little diagnostic value

Lastly one may sometimes observe in paralysis resulting from pressure on a nerve *loss of conductivity of the nerve* without histological degeneration Then the reaction of degeneration does not occur in spite of complete paralysis This occurs in tourniquet paralysis and in some cases of Bell s palsy, and means that recovery of function will be

relatively rapid Thus if in a complete or partial Bell's palsy there is no reaction of degeneration after 14 days the prognosis is excellent for complete recovery

TESTS FOR AUTONOMIC NERVOUS FUNCTION

Lack of the sympathetic nervous supply to the skin is followed by a rise in skin temperature lack of pilomotor response to skin stimulation or to a pinch of the trapezius muscle and absence of sweating in the affected area In order to clearly demonstrate the change in skin temperature the temperature of the room should be considerably below that of the body otherwise, the affected area may be cooler than the normally innervated skin The pilomotor response is irregular and often difficult to provoke

Disturbance of sweating can be demonstrated clearly by coating the skin with a compound which changes color when moistened (Minor's test) The following solution is used

Iodine	1 5 to 2 gm
Castor oil	*10 cc*
Absolute alcohol	*to 100 c c*

This is painted evenly over the skin which should be clean and dry (5) After the mixture has dried a fine rice starch powder is dusted over the painted parts with a powder puff Diaphoresis is then induced, usually by a hot drink containing 15 grains of acetyl salicylic acid and a radiant heat cradle over the uncovered skin The perspiration causes an iodine starch reaction bluish violet in color The affected area fails to change color The areas of coloration are charted

Heat sweating is more intense on the hands feet lips and forehead but it is sufficient elsewhere to outline any cutaneous area The sweating caused by *pilocarpine* and *mecholyl* is unreliable as a clinical test owing to the peripheral action of these drugs

Sweating may thus be used to confirm evidence of damage to peripheral nerves when the cutaneous distribution of sympathetic efferents closely resembles that of the nerve It will also assist in determining the segmental level of the spinal cord lesion though the limitation of the sympathetic outflow to the region between the 1st and 3rd lumbar segments must be borne in mind

Tests for autonomic function by means of the reaction to an injection of *adrenalin pilocarpine, atropine* or *acetylcholine* are not recommended as routine methods They require considerable experience in interpretation, and are subject to numerous limitations For an account of the technique the reader is referred to Monrad Krohn's 'Clinical Examination of the Nervous System' 7th edition 1938 London

THE SPINAL CORD

In diseases of the spinal cord, the following clinical findings are often present

1 *General Manifestations of Spinal Cord Disease*
   a Manifestations are bilateral although often asymmetrical
   b Manifestations only below a certain level
   c Motor or sensory impairment shows segmental distribution
   d Gait disturbances
   e Paraplegia
   f Sphincter disturbances
2 *Corticospinal Tract Manifestations*
   a Increased tonus
   b Weakness or paralysis
   c Spasticity and in long standing cases contracture may be present
   d Atrophy slight or absent
   e Tendon reflexes increased
   f Babinski sign positive
   g Abdominal reflexes are diminished or absent

   Present in
   - Multiple sclerosis
   - Subacute combined degeneration of the cord
   - Injury to the cord
   - Cord tumors
   - Syringomyelia
   - Amyotrophic lateral sclerosis
   - Friedrich's ataxia
   - Acute myelitis
3 *Spino Thalamic Tract Manifestations*
   a *Pain and temperature sensations impaired or absent*
   b Dissociated anesthesia may be present

   Present in
   - Syringomyelia
   - Hematomyelia
   - Intramedullary tumor

4 *Posterior Column Manifestations*
   a Ataxia
   b Romberg sign present
   c Tendon reflexes are not necessarily diminished or absent
   d Vibration position and passive motion impaired or absent
   e Tactile and pain sensations normal
   Present in
      Tabes dorsalis
      Subacute combined degeneration
      Friedrich's ataxia
      Cord compression or injury
5 *Anterior Horn Cell Involvement*
   a Weakness or paralysis
   b Fibrillation in the degenerating muscles
   c Atrophy
   d Tendon reflexes diminished or absent
   e Segmental distribution present
   f Rapidly degenerating muscles painful and tender
   Present in
      Acute anterior poliomyelitis
      Progressive muscular atrophy (pure form)
      Compression—usually by tumor
      Amyotrophic lateral sclerosis
      Syringomyelia

The Spastic Paraplegias

Multiple Sclerosis Multiple sclerosis is a degenerative disease principally of the cord *although it may affect any part of the nervous* system It is characterized by patchy destruction of the myelin sheaths It occurs usually in young adults of northern stock It is one of the most widespread and most puzzling diseases of the nervous system The Latin races Hebrews and Negroes are seldom affected The classic tetrad of signs—*nystagmus, intention tremor* of the arms *scanning speech* and *optic atrophy* is very seldom seen in spite of textbooks to the contrary Months elapse in large neurological centers without a patient being seen with all of these four signs There is considerable variation in the symptoms and signs owing to the unsystematic manner in which the plaques of sclerosis are scattered throughout the entire cerebrospinal axis When any cerebral symptoms are accompanied by a spastic paralysis multiple sclerosis must be suspected The commonest signs are *spasticity, intention tremor nystagmus loss of abdominal reflexes ataxia hyperactive and abnormal reflexes* To these can be added *paresthesias, anesthesias, hyperesthesias, retention or incontinence of urine*, and when the disease spreads to the brain stem, *extra ocular muscle disturbances facial paralyses* and *anesthesias* and *difficulty in phonation and swallowing* may be noted Not infrequently euphoria or less often, depression is seen in these patients Neuresthenic symptoms may occupy the foreground for months The disease is progressive and the course marked characteristically by exacerbations and remissions until finally the patient becomes bedridden The *spinal fluid* is negative except for the rather frequent occurrence of a gold curve in the so called paretic or first zone

Before making a final diagnosis consideration must be given to the absence of signs and symptoms of other conditions producing spastic paraplegias The absence of spinal block in cord tumor, of the positive serology of the syphilitic of the achlorhydria and blood picture of the combined sclerosis may be cited as examples

Course and Prognosis The disease progresses slowly by relapses and remissions and patients have been known to live their normal span The remissions may last for months or years As a general rule the course is progressive and downward Death is frequently due to an intercurrent infection cystitis, nephritis or infected trophic sores followed by septicemia

Treatment Not until we know the cause of multiple sclerosis can we hope for a specific treatment or a cure Common sense management of each case is better than much ill advised medication It would seem to depend upon which author one reads as to what form of therapy is best Very few agree which in itself seems to answer the question The following may be listed for the sake of completeness but one should remember that there is violent disagreement about many of them
   a Iron arsenic and strychnin as a tonic
   b Elimination of offending allergen
   c Vitamin B
   d Daily doses of quinine
   e Non specific protein

f Malaria
g Electric treatments and massage
h Warm baths
i Twelve to fourteen injections of typhoid paratyphoid vaccine beginning with 25 million bacteria

All seem to agree on rest and the prohibition of any physical exercise A remission may lead one to suppose that the particular form of treatment being employed at the time is successful The patients ultimately become incapacitated and require feeding and careful nursing

Spinal Cord Tumor Tumors of the spinal cord may be classified into intra medullary and extra medullary The cause of these tumors is unknown They usually occur between the ages of twenty and fifty years but they are sometimes seen in young children and the aged The most common tumors are meningiomas perineural fibroblastomas fibromas neurofibromas and sarcoma

Characteristics of Intra Medullary Tumors The earliest signs are found in disturbances of sensation which are local segmental and dissociated They are manifested by a loss of the sensations of pain and heat with a retention of tactile sensibility and the presence of the Brown Sequard symptom complex below the level of the lesion (loss of pain and temperature sense on the side opposite to the motor paralysis) The chief signs are unilateral onset with slight or absence of root symptoms, dissociated anesthesia as just mentioned paralysis on the side of the lesion sphincter disturbances increase of deep reflexes on the side of the tumor Babinski present on the affected side and a lemon yellow spinal fluid with an increase in globulin

Characteristics of Extra Medullary Tumors All forms of sensation are impaired or lost below the level of the lesion and in many cases accompanied by the Brown Sequard phenomena The chief signs are unilateral onset with early and severe root symptoms dissociated anesthesia paralysis on the side of the lesion late involvement of sphincters increased reflexes and Babinski sign on the side of the lesion and a lemon yellow colored spinal fluid containing increased globulin

Diagnosis The diagnosis of spinal cord tumor is hardly that of tumor but rather of increasing cord compression The compression syndrome manifests itself by progressive anesthesia below the level of the lesion and secondly, by a progressive motor paralysis or spastic paraplegia syndrome Since tumor of the cord is the most frequent cause of these progressive pressure symptoms, we assume such a lesion exists unless there is definite evidence to the contrary The symptoms and signs vary with the location of the tumor Those located posteriorly in the vicinity of the sensory roots cause shooting root pains in the trunk or limbs and later, loss of sensation in the painful areas followed later by the *syndrome of cord compression* namely (1) gradual progression of the disability, (2) establishment of a level above which function remains unimpaired (3) predominantly unilateral involvement (4) evidence of subarachnoid block as determined by the Queckenstedt test (see page 846) and by elevation of the *protein content of the spinal fluid* If the tumor is situated anteriorly and presses upon the motor roots muscular atrophy follows (hands and arms in cervical lesions thighs and legs in lumbar lesions) followed ultimately by the syndrome of cord compression

It must be remembered that a tumor may exist without block This is true of small tumors or in the case of tumors within the cord The level of the tumor is usually determined by the level of the objective sensory loss When this cannot be determined the *lipiodol test* may be of assistance Resulting irritation may become severe especially if there is already an inflammatory lesion Oil should not be used unless it is urgently indicated or if laminectomy seems probable, since removal of large amounts of oil except by laminectomy is difficult

Pain is the earliest and commonest complaint in spinal cord tumor It may have been present for a few years It may be at the site of the tumor it may be referred to the lower extremities but it usually radiates along the distribution of a contiguous posterior root when it is known as the root pain mentioned before The root pain has a segmental distribution As the tumor grows the pain increases and adjacent roots become involved Coughing sneezing or anything increasing the pressure of the spinal fluid may aggravate the

TABLE LVI

Diagnostic Table of the Spastic Paraplegias

(After Joughin) (6)

	Multiple Sclerosis	Spinal Cord Tumor	Cerebrospinal Syphilis	Combined Sclerosis with P A	Acute Myelitis
Age	Usually middle adult life 25 to 3 years of age	Any age especially third fourth and fifth decade	Usually middle adult life	Usually middle adult life	Any age
Course and History	Onset gradual Progress over y s *Freq t m ss s* sometime approximate et t no m l	Onset gradual Progress over months or years *No definite re m s*	*Oft n no h t y of p mary i fec t on* Course as fo tumor (Except o myelit f m)	Slowly progressive seldom r m s ons f untreated Rem s sio s po ble if consistently treated	*Rapid o set w th n a few hour to a day or t o 1 a ble re ove y* over weeks or months
Chief Complaint	Stiffness and weakness of legs *T em f ha d* V n de sed a d peech mp d May complain th t y s jerk Vague sen t ns of heat cold numbness pi d needle in e t m ties Dizziness	Stiffness and weakness of leg *Sev e shoot g oot pa* a ound tru k dow l gs Sn ez g ugh ng ncrease pa s Some times local p n in vert b ae near tumor s te Var bl genital and ph ncter disturba e	Stiffness and weakness of legs If root pa s re prese t they e les se ere th n n tumor Of t n none Som t m s heada h co vulsion dizzi s double vision etc Variable genital and ph ncter distu b nce	Paresthesias belt fo m or n hand nd fe t Achi g ndefi te pain f these parts Clum y h nds Stiffne s and weak ess of legs	P resthes as and numbness aroun l t unk and d wn limbs (Seldom severe pain Part l or c mplete paraly is below l vel of le on Vari ble g nital and ph ncter d sturb nce
Clinical Findings B	Yes—spe ch and t m r etc	Non	Rare	No e	N ne
Cranial Nerve	V s on d c ea ed Central para tral sc tomata *Pall f ptic d scs ny t gmu* e pe c ally on later l gaze (Slight p p l changes or p lysis of ex t -ocula muscl s)	No nvol ement	Sometimes involved e p c ally *p p l eact s* and e tra ocular muscles (paraly s s) d pl pia	None	In certain rare forms optic ne i ti with ptic d sc conge t on
Motor Signs	*Synd me f spast c par pleg a* S me y d om often in arms *I te t t emo f ms* (Finger e te t)	*Sy dr me of sp sti p apl gia* E ption n l mbosa r l g wths mixed or fla cid pa a pleg syndr me)	*Sy drome of p st c p apl gia* For riati ns see the d scu i n n text	*Synd me of spa t c pa apl gia*	*Synd ome f spastic pa apleg a f l lows the p ma y flac d p apl gia*
Sensory Signs	Ra ely a demo str ble patchy lo i to ch p n a d tempera t per ptio V b tory and jo t po t on nse m e affect d A sory lev l u mmo	E rly increa later decre se of sen at n in pai f l root areas *D mo strable l f pe fi ial and d ep sen b l ty b low l v l of d le S s ry lev l ex ts*	Often no d mon t able cha ge If p ese t ne e asy rono ced or learly limit d as n t mor (ex cept n my l tic fo m)	Indef n te p pher l los to t uch pa n a d tempe ature *l b at y d j t p t o* se decr ed or l st especially in f t	Senso y lo s var es below le el of l n fr m ompl te ffe ting all types to p rti l affe t ng only cert in types f se ati n Sen so y le l common
Other Findings	Sph cte and ge t l d stu b nc s rar ex pt n ad n ed es *Spe h t ds t be sl lab pl m it d w th d ffic lty*	At phy and par lysis Ro t p s in c vic l nd l mbar c d	Po bly l al h nc e sc r or ther g s of p st l etic l fect n	C *iltut l g s d y npt m f per t nem* (gl it l mon l r t k n tc)	Fev r cc ally Syst mic r l cal i f t n m y st (Oft n v k wn)

L bo t y Sp (Fl 1	Us lly norm l I l ge pe nt the g ld c r p t t lu t typ W s m g t	Sp al block u gl b l p e t p se n s d fl ld y ll w J t C lls bo l n m l (0 t 8)	H s ma n p t e 50 to 80 p c 10 pend g po typ f t I ase in gl bul a d p ol Fl d olly l a Cells a d t h d eds	No m l	Fl d ct ae Na bl c e in c ll a d p ote n o fl d no m l
Oth R po t	Blood W erm n n g t e	L p od lm y d c t t morl l	N r lated f d g Blood po t 50 to 80 (p r nt	Bl d p t e f P A m e o l ss cl (s ll yp e d d d ymp t m) A hlo hyd t 90 l 95 pe c t Norel ted o e tge f d g	Blood p ture may s gg t e t t g nl ct s p No el ted tg f nd g

	Tr m of the Co d	Lower Cervi l C d Syndr me	Tub culo s Sp n l Ca s	V t b al Mal g a cy
Age	A y age b t mo e mm n in ad lt l l	Sy t g m) l a 15 t 30 Am) t pk l t tr l s l o t 35 t 50	Ch l le a d y u g l lts	Ad lt l l
C r e d H a t ry	R p d o t ml t a to h Rec ry sform) l t H l y f t) y s lly bl bl	S) t g m) f a \ t bl te f p g e P q e t rr t D e ti a j s to l f f m ALS L (h l l f to 5 ye rs	Sl p gr loa t p r pl g R l g es a d i ol a y t me R lap e not mm n	Rap d p og e s N r mitt n e r a rest Symp m le el p u u lly t Bon 2 Ro ts 3 C d
Ch f Compl t	Pain at s te I nju y Other s mptoms e y sim la t th e of my l t s	Inh (kd se W ak e s t ng of h n) mu l St ff e d w akn s t l g Sy t g m) lt Bu p l ks t ts h m lf th t p l ALS P og t e in bl lty to rt ulat a l)	l e t b al p o se n gh b a g) r t g mo ng spi e (Imm l l ty e te r du e p) Stiff ess of sp St ff n ss a d weakn s t legs Radiat ng root pa l t v ry comm n	Pa n) sp nal c l mn Age l g o t pa s St ffnes a d w akn ss in l gs
Cl t al F d gs Bra n	N n u l a c c m ts (l ra n nj ry	N	No e u l s intracr l ompl c t ns	Non u l s b at meta ta s
Cr l N s	S me l e	S) c m) l a P olj a d l oph f the t g e n t S m t m s e y los f tch a ALS P r l) s s f c l r ds p lat fh r t g l ps omm Atr phy a d fib ll t s f th m les	S me a abo e	S m a ab e
Mot r S g s	ta f c la m) l t s	S) a d ALS Sy d me f pa l p apl s At phy and fib ll t l s f pa ly ed m s l s (p lly a ms and ALS) I c ea d r fl es tms in ALS	S) d me f p u p pl gl	Syndr m I p t c pa apl g a t pr ed n d only l the p tie l l s) g enough
S ry Sig s	A f r a tem) l t S) t g m) l d so t a ll r t al l m tlag (h ma t m) l) B) Sequ l y l m at t mes gg t l	S) gomyel a Pe pll n f h ot c ld p l sl l mu h l d To h n a ly f ALS No h) l e r y d s t b	D m strable en y lo s ta e (s e ca es ly)	Obj cti s n ry l s n t c mm nd d fin te e y le l n
Oth r l) l gs	Sig f l (t n No f e l l)) r) lll s f tl	S) e s ll Kyl l l Oft n s m l d ll b a I t b thd s a s H n s y d ome at tim S t t	l g lar d f m ly g lb T b c lo is cl cule l a ly sp al t ll s l ecal g tempe tu e l ?	H spl) lef mity lly o l) t c ti n H l g n y else h e

TABLE LVI—*Concluded*

	Tr uma of the Co d	Lower C ical Co d Syndrome	Tuberculos s Sp nal Caries	Vertebral Mal gna cy
Laboratory Sp al Fl id	Fl id cl ar to *bloody* Cells prote n etc ary widely Som times co d comp ession p ct re with blo k	In *b th* no mal	No mal or may ha e y drome f p rti l or complete block	Norm l or y d me of part l block Compl te block not common
Othe Reports	Defin te ro ntg n d ce in vast majority of patients of vertebral injury	*Syr g myeli* Vertebral d f rm t s on roentge t dy *A L S* No r lat d fi d gs	Demo trat n f Koch bacilli fl ds and tissues Ro tgen evidence of th n g of intervertebral d s Erosion of adjace t vertebral margins Later exten e de struction of body	Demonstr t n of mal gna cy in other tissues and fl ds *Roe tg n vide ce of ero s on f ve teb ae* ribs or ther skeletal str ctures

pain Root pain may awaken the patient at 3 or 4 o clock in the morning when he finds that he can secure relief by anything that shortens the spine, such as walking or sleeping on a chair A useful test consists in flexing the head sharply on the thorax This maneuver will often accentuate the pain Inspection of the patient s shoes may show a decided difference in the amount of wear It is not uncommon for patients to collapse suddenly, arise and wonder why they fell This may be associated with dumb bell shaped tumors which lie partly within and partly without the cord and cause transient compression

Treatment Medicinal treatment is merely symptomatic and by itself can offer little for the pains are often intractable and not relieved by narcotics Deep roentgen therapy may be used in a few types of irremovable tumors or postoperatively The treatment is surgical

Syphilis of the Spinal Cord Syphilis is an important cause of degeneration of the posterior columns of the cord The advanced full blown clinical picture of tabes is not as common today as it was some years ago Syphilis of the cord rarely exists alone The brain is usually involved and the condition is really one of cerebrospinal syphilis Three main clinical groups are described

1 Progressive spastic paraplegia of an almost pure type, with minimal subjective and objective sensory disturbances Paraplegia develops very slowly the onset occurring usually some years after the date of the initial infection The damage is principally to the pyramidal tracts

2 Progressive spastic paraplegia associated with or preceded by root pains over a period of weeks or months indefinite sensory loss in the painful areas and perhaps spinal rigidity and tenderness (chronic syphilitic meningitis) This type of spinal syphilis is perhaps that most commonly met with It ordinarily develops earlier and progresses more rapidly than the purely spastic type The sensory disturbances are due to involvement of the meninges, with consequent root irritation The resemblance of this form to spinal tumor is sometimes striking

3 Progressive spastic paraplegia developing weeks or months subsequent to an acute flaccid paraplegia (acute transverse syphilitic myelitis) The subsequent course is that of an ordinary acute myelitis The syndrome is usually due to thrombus formation in diseased arteries with resultant paralysis and myelomalacia

Symptoms and Signs *Lighting pains* are almost pathognomonic of parenchymatous syphilis of the cord, though they are, in rare instances, encountered in diabetic neuritis, syringomyelia and in apparently normal persons They are sharp, short and spot like and appear in showers often in the same spot during the same shower They are usually present in the lower extremities and may leave the skin hypersensitive to light touch but not to heavy pressure *Crises* are suggestive of neurosyphilis but they may also occur in migraine angioneurotic edema, or they may be familial in origin They occur most commonly in the abdomen but they may occur in the eyes larynx or rectum There is a sudden onset with pain or vomiting or both extreme nausea and sialorrhea, the pain is usually near the mid line and has been described as dull, sharp aching cramping squeezing or burning mild or excruciating It may last from hours to days and usually terminates suddenly There is hypersensitivity to the lightest touch The *signs* are Argyll Robertson pupil, absence of the patellar or Achilles tendon reflex absence of pain on pinching the calf, delay in the appreciation of painful stimuli

Diagnosis The diagnosis of spinal syphilis is based upon

a A history of specific infection This is often lacking
b Existence of signs indicating intracranial involvement (pupillary involvement)
c Blood or spinal fluid findings indicating the presence of syphilis

Treatment For further discussion on diagnosis and treatment the reader is referred to page 403, 408–410

Neuroanemia (Subacute Degeneration of the Spinal Cord—Postolateral Sclerosis) This is the most frequent disease of the spinal cord associated with nutritional deficiency It is frequently associated with pernicious anemia but it is often found also in infections intoxications and vitamin deficiency states Degeneration of the dorsal and lateral columns,

sometimes of other tracts, the peripheral nerves, and rarely, the cerebrum characterize the disease

Signs and Symptoms The onset is usually insidious and the neurological manifestations may appear either before or after the development of anemia or other non neurological indications of the disease Peripheral subjective sensations occur early and are felt in the distal portions of the limbs, but they may be experienced in the perineum, neck, occipital region or in the tongue Sensory disturbances of a "stocking and glove" type of distribution begin in the limbs and ascend in segmental fashion upon reaching the trunk Vibration and position senses are affected early and tenderness of the calf muscles and plantar surfaces is an almost constant finding The peripheral subjective symptoms are tingling and numbness smarting burning and creeping sensations In some cases icy coldness and lighting pains similar to those of tabes are felt There is marked asthenia following any exertion Loss of sexual drive and power is commonly present and may occur early in the disease The deep reflexes especially of the lower extremities are exaggerated The gait is typical, the patient walks on a wide base with legs spread apart and eyes fixed on the ground or shows definite ataxia, the legs are spastic, occasionally flaccid There may be a generalized atrophy of the muscles in the affected limb A positive Babinski sooner or later may be found The tongue is clean and usually smooth and red Anemia may be absent throughout the disease but in about 50 per cent of cases it is conspicuous at the time of onset of the nervous symptoms Mental deterioration drowsiness or mild delirium may occur Dimness of vision nystagmus and pupillary abnormalities have been observed

The Blood Picture The blood picture usually shows a primary or macrocytic anemia the color index is higher than normal and may reach 1 6 A relative lymphocytosis and variations in the size shape and coloration of the red cells are common Normoblasts are numerous and megaloblasts may be found Nearly all the patients have achlorhydria

Treatment *Liver* therapy is essential and treatment should be directed toward keeping the red blood cell count as close to five million as possible It is better to give too much than too little *liver extract* and daily intramuscular injections, 25 to 50 international units, are advocated for the first week This dose may be given only every other day in the second week and twice weekly thereafter up to and including the tenth week A weekly maintenance dose may then suffice Lightning pains are treated with intravenous injections of *atropine sulfate* grain $\frac{1}{100}$ *to grain* $\frac{1}{50}$ *(0 6 to 1 2 mg)*

Myelitis Myelitis is an inflammatory condition usually localized and involving an entire transverse section of the cord When it is limited *to a few segments it is called transverse myelitis* if it spreads upward it is called ascending myelitis It is commonest in the dorsal region because this part of the cord is longest and poorest in blood supply

Etiology Acute myelitis is usually a toxic, infectious process following or occurring in the course of acute infectious diseases such as *measles scarlet fever diphtheria, influenza erysipelas, varicella, endocarditis, pneumonia gonorrhea* or *pertussis* It may be pyogenic or occur in the course of pregnancy or diseases of the urinary tract It is frequently a part of neurosyphilis The patients often have a fever but there are few reliable clinical phenomena which can aid one in the differentiation between inflammatory and non inflammatory conditions

Symptoms For a period of some days the patient complains of paresthesias and weakness in the legs and then within a few days a flaccid paraplegia develops with loss of tendon reflexes loss of sensation below the level of the lesion and genital and sphincter disturbances There is retention or incontinence of urine and in some cases constipation The patient complains of a "band" around the body with pain numbness and tenderness The feces are retained and sex power is lost if the lesion is in the lumbar region A thoracic or a cervical lesion may cause priapism If the lesion is above the lumbar area a spastic paraplegia with increased tendon jerk will be apparent if in the lumbar region the paraplegia will be flaccid with loss of reflexes The skin temperature is lowered in the legs *the skin is rough* and in some cases is covered with sweat The prognosis is unfavorable if the body temperature is

elevated If the lesion is limited to one half of the cord a Brown Sequard syndrome may be present Bed sores may develop rapidly over the sacrum and great trochanters In cases of cervical involvement a flaccid paralysis develops in the upper extremities and spastic paralysis in the lower If the lesion is at the level of C3 or C4 there may be complete spastic quadriplegia with paralysis of the diaphragm *Myelitis of the conus* gives paralysis of the bladder and rectum and saddle anesthesia

Diagnosis In the beginning it is very difficult to differentiate myelitis from meylomalacia caused by thrombosis of the spinal vessels The diagnosis is usually based upon (1) the acute rapid onset (2) rapid advancing paraplegia (3) impaired sensation below the level of the lesion and (4) early sphincter involvement

Differential Diagnosis

Syphilitic Myelitis The blood and spinal serologic tests may be positive Signs of neurosyphilis may be present

Compression of the Cord Course is slower and pain prominent Subarachnoid block may point to the cause

Multiple Sclerosis The progress and incidence of multiple lesions are characteristic See page 882 884

Polyneuritis Flaccid paralysis the pain is more severe the reflexes remain absent and there are episodes of extreme tenderness along the nerve trunks The sensory disturbances are limited to the distal portions of the extremities There are no disorders of rectal or bladder functions

Acute Disseminated Encephalomyelitis There are mental symptoms pupillary changes and optic neuritis meningeal signs and abnormal involuntary movements

Treatment The treatment varies with the cause of the myelitis The care of the skin is most important Scrupulous attention should be given to bony prominences and pressure minimized by the use of an *air mattress competent nursing* freedom from dampness caused by sweating or incontinence As sensation is impaired the use of electric pads or hot water bottles is fraught with danger *Tidal drainage* is of use when constant catheterization is necessary Regulation of the bowels should be by *enemas* which if given daily will prevent soiling In spite of the best of care and attention bed sores will develop They are treated with *zinc oxide powder, tannic acid* and *orthoform* A *bed cradle* is useful since it keeps the bedclothes from contact with the legs which are hypersensitive and easily excited to reflex sweating The legs should be moved as little as possible When recovery is apparent *massage* and *warm baths* may be given The *galvanic current* may be employed after the acute stage has passed and is of some value in flaccid paralyses Foerster has shown that in selected cases cutting the posterior roots is helpful for late spasticity When syphilis is the cause active treatment should be given

Trauma Trauma of the cord is usually associated with lesions of the vertebrae If the injury is sufficiently severe the clinical picture may be that of a complete transverse myelitis or of a mild spinal concussion Trauma of the cord frequently results in the development of a paraplegic syndrome similar to that described under myelitis The spastic syndrome develops gradually some weeks subsequent to the initial flaccid paralysis which if the lesion is severe immediately follows the trauma Occasionally flaccid paralysis does not appear the spastic paralysis developing gradually as a result of callus formation or of a slowly increasing and organizing blood clot With hematomyelia the sensory findings may be similar to those of syringomyelia

The spinal column may be fractured without its causing any neurologic symptoms or signs Injury to the cord occurs in about one third of the cases of spinal fracture The injury may cause intramedullary disintegration and hemorrhage without compression There may follow an associated shock like state which lasts for from four to five weeks The sphincters are usually contracted for a variable length of time following the injury They may subsequently relax and remain so or a period of involuntary action may ensue

Treatment The treatment of spinal cord injury is conservative Injury to the cord has been compared to the results of dropping a glass tumbler on the floor the damage is immediate and is often irreparable The only exception is when the patient is seen almost imme

diately following the accident whereupon an attempt may be made by decompression to relieve the pressure The results of operation are seldom good, for the damage has been done If roentgenograms show marked overlapping of the bone and give evidence of complete shearing of the cord nothing can be gained by operation If the vertebrae are in fairly satisfactory alignment and a spinal puncture gives no evidence of a block, operation is unnecessary If the vertebrae are in satisfactory alignment but a block is present, laminectomy may do good The general care of the patient is very important and should follow the principles set forth under the treatment of myelitis See page 889

Cervical Cord Syndromes

1 *Spontaneous Hyperemic Atlo Axoid Dislocation* Woltman (7) has called attention to the fact that frequently this type of injury is not properly understood The atlas moves forward on the axis and when the dislocation is marked, the odontoid process or the transverse ligament gives way, the pyramidal decussation is pressed upon causing paralysis without loss of sensation The paralysis is more marked in the arms than in the lower extremities Treatment involves skeletal traction to insure stability of the cervical spine for laminectomy wherein the arch of the atlas is removed relieving pressure on the cervical cord The cervical vertebrae are then fused by a bone graft

2 *Lower Cervical Cord Syndrome* A destructive lesion involving the eighth cervical and first thoracic segments or their motor roots produces paralysis and atrophy of the small muscles of the hand with degenerative fibrillary twitchings and miosis due to the unopposed action of the constrictor pupillae The miosis is usually associated with a slight ptosis and enophthalmos (*Horner s syndrome*) The association of these two groups of symptoms constitutes an important localizing syndrome for this portion of the spinal cord

3 *Syringomyelia* Syringomyelia is an intrinsic degenerative disease of the spinal cord appearing usually in middle age and giving rise to atrophies fibrillations trophic disturbances spasticity scoliosis and disturbances of pain and temperature senses The cause is unknown, but its relationship to intramedullary tumors is close since about 50 per cent of these are associated with syringomyelia The disease is characterized by the formation of cavities within the cord and medulla The cavitation is preceded by gliosis which undergoes cystic degeneration

Symptoms and Signs Paresthesia and loss of pain and temperature sensations appear first The patient may unconsciously burn himself There follow weakness atrophy and fibrillary twitchings first noted in the interosseous muscles The muscles in the arms and neck later become involved Numbness and painful tingling are common sensory manifestations Although the disease is usually bilateral, one side usually shows greater damage than the other The *reflexes* are diminished or lost Trophic and vasomotor disturbances appear such as, excess sweating edema of the soft parts coarseness of the nails and indolent ulcers on the fingers Sometimes one may see perforating painless ulcers and arthropathies not unlike those seen in tabes dorsalis (Charcot s joint) Syringomyelic lesions in the lower cervical region produce the typical Horner's syndrome which has been described An almost constant secondary sign is that of scoliosis When cavitation involves the medulla the condition is called *syringobulbia* It causes paralysis of the palate, uvula or vocal cords paresis of the tongue, with atrophy and difficulty in swallowing Involvement in this region may give the symptoms of anesthesia in the distribution of the trigeminal nerve on one side of the body and loss of pain and temperature on the opposite side

Diagnosis This rests upon the following signs

1 Loss of pain and temperature sense in certain areas
2 Localized muscular atrophy and fibrillations
3 Trophic ulcers
4 Scoliosis
5 Partial or complete subarachnoid block
6 Dissociated sensory disturbances of a waistcoat distribution
7 A long course

The diagnosis should always be considered in those conditions that do not present a clear clinical picture of (1) Multiple sclerosis, (2)

Amyotrophic lateral sclerosis, (3) Neuroanemia or subacute combined degeneration (Posterolateral sclerosis) (4) Progressive muscular atrophy

Course and Prognosis The course is usually prolonged in some cases for forty years Death generally results from bulbar involvement



FIG 174 Syringomyelia Note Destructive Bony Changes

Treatment The treatment is symptomatic Even slight burns should be avoided in view of the poor healing Treatment is restricted largely to surgical drainage of the distended cord and to roentgen therapy Surgical drainage is indicated when spinal puncture discloses blockage of the subarachnoid pathways Little permanent benefit will be derived from deep x ray therapy but it may relieve the pains Recently laminectomy has been suggested for the purpose of evacuating the syrinx decompressing the cord and facilitating treatment with deep x rays

Amyotrophic Lateral Sclerosis This is a degenerative disease of the spinal cord It is characterized by lesions in both the upper and lower motor neurones (degeneration of the long descending motor tracts and anterior horn cells) It is closely associated with progressive muscular atrophy and bulbar palsy and all three are considered as the same disease in different parts of the nervous system This is a fatal disease which runs a subacute or chronic course and usually affects patients in middle age Males are more often affected than females

Clinical Manifestations The onset is insidious and is characterized by bilateral weakness of the small muscles of the hands The upper extremities usually become wasted and the lower extremities spastic There is awkwardness in using the fingers In the majority of cases the thenar and hypothenar eminences are involved first Fibrillation appears early and atrophy follows as the process spreads in the upper cervical spinal cord The shoulder girdle muscles next become involved and the tongue may follow with typical atrophy and fibrillation Speech becomes indistinct and slurred and food may be regurgitated through the nose The muscles may respond to the faradic current even when they show marked atrophy and fibrillation With involvement of the pyramidal tracts there will be spastic paralysis of the legs with increase in the deep reflexes ankle clonus and bilateral Babinski sign As a rule sensation remains unimpaired and the sphincters continue to function

Progressive Muscular Atrophy In this condition the *lower motor neurone* alone is involved The disease usually begins in the hands progresses to the shoulder, the chest and finally into the legs The reflexes are diminished or lost The clinical picture is principally one of weakness, paralysis, muscular atrophy and fibrillation There is no sensory involvement The disease is very slowly progressive and may last for years before death supervenes The human skeletons seen in circuses are for the most part cases of progressive muscular atrophy

Bulbar Palsy This disease starts in the medulla, usually at the level of the 12th cranial nerve It usually can be recognized by atrophy of the muscles of the face jaws and tongue, with difficulty in phonation and swallowing *In pseudo bulbar palsy* the lesion is usually in the internal capsule or cortex There is loss of control over emotional reactions, the patient laughing when he is sad and crying when he is happy Pseudo bulbar palsy is a syndrome rather than a disease in itself The *diagnosis* is based upon a history of two or more attacks of a partial or complete hemiplegia, the presence of bulbar symptoms *without paralysis atrophy electrical changes* speech disturbances spasticity, bilateral pyramidal tract signs and upon the emotional reactions already mentioned

Treatment The treatment is symptomatic Tubal feeding may be necessary in those with bulbar palsy *Vitamin E* has been recommended by some who have seen some benefit from its use Wechsler prescribes 50 to 100 mg daily and a diet rich in vitamin E

Tuberculous Spinal Caries Caries of the spine is one of the most frequent causes of spastic paraplegia It is almost always secondary to bone, gland, genitourinary or pulmonary tuberculosis It occurs most frequently in the dorsal spine, though not infrequently in the lumbar vertebrae *and in the cervical region* It is most common in children and young adults It has been found in infants and may be evident even at birth Trauma to the spine may be an exciting cause The characteristic *angular* gibbus' deformity is usually present in the later stages Deformity may exist without paraplegia, or, the paraplegia may exist without deformity The pressure producing the paralysis is usually due to a cold abscess or a pachymeningitis *rather than to pressure* by a diseased or displaced bone

Symptoms The first symptom is usually localized *pain*, dull and boring, and aggravated by jarring or movement There may be *local tenderness* to pressure, usually limited to an area over one or two spines Reflex rigidity of the spine will be found and the patient may hold his spine rigid in a characteristic fashion or in the case of cervical spondylitis, support his head with his hands Any immobility such as recumbency relieves the pain However, as the protective muscle spasm which immobilized the spine during the day time wears off, the pain may return and is often significantly worse at night Neurologically, the clinical picture is one of gradual cord compression as previously described except that the root pains and objective sensory disturbances are not so severe Striking improvement even to the extent of an apparent cure may occur in a severely paralyzed patient This is met with in no other type of cord paralysis

Diagnosis This causes no difficulty and is based upon

1 Familial and personal history
2 *Temperature rise in the evening* (possibly)
3 Early spinal pain and rigidity
4 Discovery of other tuberculous foci
5 Local deformity and tenderness
6 Roentgen findings

The Flaccid Paraplegias

Flaccid paraplegia is a term signifying paralysis with muscular tonal loss The paralysis and loss of muscle tone is most marked *when it is the result of a lower motor* neurone lesion Paraplegias presenting the complete syndrome of lower motor neurone lesions are classified as *true* flaccid paraplegias, those presenting the incomplete syndrome are termed *pseudo* flaccid paraplegias

True Flaccid Paraplegias

Poliomyelitis
Multiple Neuritis
Cauda Equina Lesions
Landry s Paralysis

Pseudo Flaccid Paraplegias

Tabes Dorsalis
Conversion Hysteria

Muscular Dystrophy (Leg type)
Peroneal forearm atrophy
Infantile Atrophies
  a Amyatonia Congenita.
  b Werdnig Hoffmann

Poliomyelitis This is discussed under Infectious Diseases The reader is referred to page 725 for a full discussion

degeneration predominates and peripheral neuritis to the smaller group in which there is actual inflammation with exudative changes To quote Wechsler (8)

'The evidence thus far accumulated justifies the following tentative conclusions (1) Many cases of multiple neuritis of obscure etiology are probably neither toxic nor infectious at least not in the loose

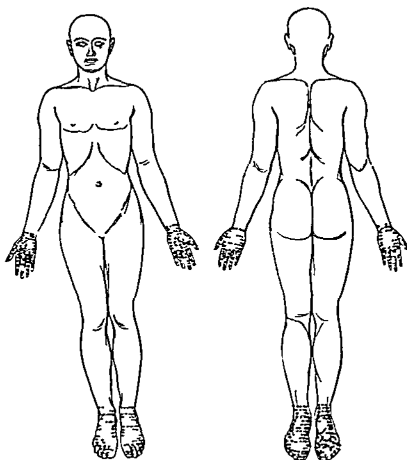


Fig 175 Multiple Neuritis Illustrating Glove and Stocking Type of Anesthesia

Multiple Neuritis Multiple neuritis is a degenerative disorder of the peripheral nerves due to a variety of exogenous and endogenous causes The commonest are those caused by bacterial toxins chemical agents vitamin deficiencies and the residuum of non specific neuritis

General Considerations Wechsler suggests the substitution of peripheral neuropathy for the term neuritis It could be applied with accuracy to the majority of cases in which

sense in which those words are sometimes used but more likely are deficiency syndromes This view is fortified if in a given case one elicits a history of prolonged loss of appetite diarrhea or vomiting or one find absence of free hydrochloric acid or other evidence of gastric intestinal or hepatic disturbance It is worth bearing in mind that for faddist or other reasons people sometimes deprive themselves of various food stuffs and that even otherwise adequate regular diets may be deficient in vitamins so that individuals unknowingly suffer from avitaminosis The therapeutic test can be and often is of great aid in such cases (2) In many cases of polyneuritis which have hitherto been regarded as due solely to specific causes such as

alcohol diabetes arsenic lead one finds an additional possibly ultimately determining factor in avitaminosis This may be due to involvement of the liver or gastrointestinal tract of which not infrequently there is clinical evidence (3) The fact that the general pathological changes are degenerative rather than inflammatory and similar to the degenerative changes seen in avitaminosis is of considerable clinico pathological significance Hence the need for substituting the term neuropathy for neuritis (4) While there is definite evidence that the absence of the antineuritic vitamins B_1 and B_2 or G is responsible for many of the cases there is experimental proof for the assertion that absence of vitamins A and E and even C and D may also lead to degeneration of the spinal cord roots and nerves and that their presence will prevent degeneration by poisons which sometimes affect the nervous system That there are however true instances of multiple neuritis on the basis of infection and with the pathology of inflammation where neither avitaminosis nor poisons come into play is beyond any doubt

Symptoms The general symptoms of any type of neuritis are (1) pain on pressure along the course of the nerve (2) impairment of touch, pain temperature vibration and position sense, there may be hyperesthesia or hyperalgesia (3) motor impairment ranging from mild weakness to complete paralysis, (4) atrophy in the parts supplied by the nerve, (5) loss of deep reflexes, and (6) vasomotor and trophic changes viz congestion edema, dryness sweating keratitis desquamation and atrophy of bone

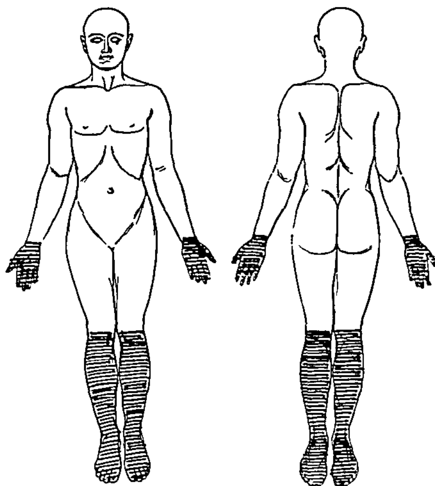


FIG 176 Peripheral Neuritis Illustrating Glove and Stocking Areas of Cutaneous Paresthesia

The legs are affected most frequently and severely The initial complaint is usually numbness tingling or a pricking sensation in the feet or hands which is soon followed by weakness in the distal parts of the extremities Severe paresthesias follow the paralysis in

creases and ascends the extremities to involve the proximal portions of the limbs In the early stages there is increased sensitivity to all stimuli Later there is seen a loss or decrease in the sensory response which is usually of the glove or stocking type, it is seldom complete and is most marked distally, the hyperesthesia and hypalgesia gradually fading away toward the trunk The paralysis affecting all four extremities is usually symmetrical both in respect to the extent of involvement of the limbs and muscle groups affected This is to be contrasted with the inequality of function in the paralyzed limbs of poliomyelitis

Not all forms of polyneuritis are alike in their manifestations Different poisons have apparently, an affinity for certain nerves or even portions of nerves or for the brain The cranial nerves are usually spared

Alcoholic Polyneuropathy In adults this is fairly common and from the standpoint of neuritic symptomatology it is the most complete Prodromal symptoms may last for weeks with numbness and tingling prominent and tenderness of the nerves and muscles There may be mental confusion before numbness is observed There are slight pain and weakness in the lower limbs The fingers hands and arms are affected as well and the skin becomes reddened and edematous The muscles become weaker and the patient cannot stand In a few weeks there is loss of power in the leg *foot drop* may follow from involvement of the anterior tibial nerve *Wrist drop* may appear later Rarely the 1st 3rd 4th 5th and 6th cranial nerves are involved After from 10 days to 2 weeks the foot and wrist drop are fully developed there is paraplegia and muscle atrophy as well as slight edema about the feet and legs The skin and deep reflexes are lost There is some tactile anesthesia with hyperalgesia Sensory impulses are transmitted slowly The reaction of degeneration sets in with partial or complete loss to faradic stimulation and lessened response to galvanic stimulation In alcoholics there may be mental confusion or a low muttering delirium *Korsakoff's syndrome* of confusion confabulation and hallucination may develop After two weeks the condition starts upon a chronic course Alcoholics show great prostration and are likely to contract pneumonia and die particularly if the right upper lobe is involved If they are ambulatory they may have a step page gait Most of the patients recover though it may be from months to a year before recovery is complete foot drop and contractures may persist as a residua

Lead Neuropathy See page 695–697

Diphtheritic Polyneuritis This condition is almost unknown in adults but it occurs in children It is seen rarely when the antitoxin has been given on the first day of the disease and is worst in those cases in which the serum has either been given late or not at all The neuritis usually appears several weeks after the onset of diphtheria The first sign is usually a regurgitation of fluids through the nose and a loss of sensation over the palate There is paralysis of the uvula the soft palate and in some cases, there may be paralysis of accommodation with varying degrees of ptosis and paralysis of the ocular movements This may last a few weeks and end in recovery The bulbar nerves are sometimes more severely affected in which case the laryngeal and pharyngeal muscles become paralyzed and there is anesthesia of the mucous membrane If the vagus is paralyzed the pulse may be rapid or there may even be heart block Phonation, deglutition and breathing become difficult In bilateral phrenic paralysis the dyspnea is severe and death usually results Generalized polyneuritis may supervene with involvement of the hands shoulders and thighs The paralysis is the atrophic flaccid type electrical changes are present and the deep reflexes diminished or lost There may be degeneration of the pyramidal tracts with a bilateral Babinski sign also ataxia steppage gait, foot drop and impairment of sensation Hemiplegia may occur, and occasionally early in the disease there may be signs of meningeal irritation with moderate stiffness of the neck and a positive Kernig's sign The *prognosis* is generally favorable if cardiac or respiratory nerves are spared

Arsenic Polyneuropathy This condition is usually the result of a suicidal attempt the prolonged use of Fowler's solution occupational hazards or of treatment with arsphenamine The neurological manifestations are similar to those seen in alcoholic polyneuropathy The lower extremities are usually

affected first, there s motor weakness in the feet and calves extreme muscle tenderness on pressure as well as muscle cramps and aches, and diminution of ankle and knee jerks Since the sensory fibers are affected ataxia is a prominent symptom Dermatitis exfoliativa, herpes, pigmentation of the skin, erythema and edema of the limbs are common Optic atrophy may occur *Antimony* and other heavy metals give practically the same clinical picture

Diabetic Polyneuritis It is doubtful whether this is a true neuritis pathological studies point to its being of arteriosclerotic origin It is seen in elderly diabetics and is believed by some to be a neuropathy related to a disturbance in the lipoid and sugar metabolism Referred pains due to an accompanying osteo arthritis are not very uncommon The paralyses do not run a parallel course with the severity of the diabetes, they are not severe and recovery is the rule

Infectious Neuritis This condition is an acute symmetrical process involving the peripheral nerves and more rarely the spinal cord and the brain It is often associated with infections of the upper respiratory tract Sensory disturbances are common and usually involve the distal portions of the extremities The disease is accompanied by fever chills leucocytosis, cranial nerve palsies and a gradual progressive involvement of most of the peripheral nerves with numbness tingling pain motor weakness and a diminution or loss of the reflexes Bilateral facial palsy frequently occurs The infectious process may involve the anterior horn cells and a spinal fluid examination may reveal the presence of increased cells and globulin The paralysis is flaccid and atrophic in type

Differential Diagnosis

Anterior Poliomyelitis The disease is less extensive, sensory symptoms are less prominent and atrophy is more evident

Landry s Paralysis Sensory symptoms are usually absent

Myelitis Babinski s sign a sensory level and involvement of the sphincters are present

Prognosis When the respiratory muscles are involved the mortality is high Otherwise the prognosis is good

Less Common Types of Neuropathies

Ginger Paralysis This form of polyneuritis follows the ingestion of ginger extract adulterated with triorthocresyl phosphate Changes in the peripheral nerves and spinal cord are severe and result in wrist and foot drop as well as atrophy of the affected muscles The treatment is that of a generalized polyneuritis

Hematoporphyrinuric Polyneuritis This often follows the ingestion of veronal sulphonal, or trional Abdominal pain often may be of such severity as to suggest an acute surgical abdomen The mortality may be as high as 50 per cent The diagnosis is confirmed by finding hematoporphyrin in the urine The treatment is that of a generalized polyneuritis

Thallium Acetate Polyneuropathy This follows the prolonged use of depilatory pastes containing thallium acetate It is characterized by cranial and spinal nerve palsies, clouding of the sensorium confusion disorientation convulsions and choreiform twitchings A careful history and analysis of the paste may aid in the diagnosis

Mercurial Neuropathy This is similar to other forms of polyneuropathy, but the diagnosis will usually be clear from other signs of mercury poisoning viz, (1) stomatitis and gingivitis (2) salivation and fetor oris, (3) diarrhea and anorexia, (4) albuminuria and hypertension (5) intention tremor

Sulfonamide Dermatitic Neuropathies The sulfonamide drugs may cause transient involvement of a single or of several nerves

Erythredema Polyneuritis This disease sometimes called Pink Disease occurs in infants or small children and in small epidemics The cause is not known The clinical course is characterized by apathy restlessness anorexia insomnia rash, sweating dermatitis and vasomotor changes consisting of redness and swelling of the face fingers and toes desquamation of the palms and soles, and in some cases trophic ulcers The muscles are mildly flaccid and the reflexes are lost The course of the disease lasts for eight months and treatment consists in adequate nursing and feeding

Post Hypertherm Neuronitis This condition is due to a relative vitamin deficiency resulting from the increased vitamin metabolism in the course of protracted fever It has been reported in cases undergoing prolonged

hypertherm therapy The clinical manifestations run the gamut from slight weakness and cramping of the muscles of the lower extremities to a severe generalized neuritis with pain loss of reflexes and marked weakness Examination of the spinal fluid has revealed an elevated protein content

General Mangement of Multiple Neuritis and Neuropathy The most important single factor in the treatment of the toxic neuritides and of those due to chemical or poisonous agents is the removal of the cause This may entail the use of gloves in painting the cessation from association with noxious agents and possibly the change of occupation When alcohol is the cause it should be withdrawn immediately unless cardiac failure or delirium tremens is feared when it should be tapered off gradually The treatment of the neuritides associated with nutritional deficiencies is discussed on page 33 Needless to say any metabolic and deficiency states must be corrected In such diseases as *syphilis* or *diphtheria* the underlying cause should be treated with specific therapy and without delay The *general treatment* of the paralyzed muscles to prevent overstretching and the formation of fibrous tissue is of paramount importance Owing to the concepts recently introduced by Sister Kenny and which are still subject to controversy the treatment of weakened and paralyzed limbs is in a state of flux The Sister Kenny treatment is discussed on page 726 The nutrition of a muscle deprived of its nerve supply may be maintained by artificial movements which can best be supplied by the galvanic current The slow wave like contraction thus produced is an excellent means of massaging the involved muscles Electrical treatment is started as soon as muscle and nerve tenderness has disappeared, and should be continued until the faradic response and voluntary power return In cities patients may go to clinics where trained physiotherapists working under medical supervision instruct the patients and their relatives in what to do in order to restore maximum function This is not possible in rural disticts but in these days of rapid transportation it may be advisable to send the patient for a week to some nearby urban medical center where those who will look after the patient when he returns home will learn the essentials of treatment In severe cases each paralyzed muscle should be gently stimulated with the galvanic current eight or ten times three times a week Arms and legs may be treated on alternate days If there is anesthesia care must be taken not to burn the skin Gentle massage with the splints removed should precede each treatment by electrical stimulation for a period of from five to ten minutes Maximum responses will be seen at Erb s points and the progress of the patient can be recorded from week to week by the changes in the responses *Heat* in the form of diathermy is often soothing In the Kenny treatment *hot moist packs* are used *Counter irritants* are of use especially methyl salicylate and chloroform liniment which are often comforting when they are applied locally by light massage *Aspirin* may be used and in severe cases may be combined with codeine If the neuritis is acute the patient should be put to bed Infected foci should be sought and removed unless there are no contraindications One should look for signs and symptoms of cardiac failure in which case digitalis may be necessary Pernicious anemia should be treated Achlorhydria calls for *hydrochloric acid* 15 minims three times daily An air mattress is a great comfort A cradle should be used to support the weight of the bed clothes In any case *orthopedic care* and *physiotherapy* as described above are necessary in order to prevent the development of deformities and contractures Contractures at the knee can be avoided by keeping the legs extended A foot board or sand bag or both may be used to prevent contractures of the toes and of the Achilles tendon

Diphtheritic Paralysis If paralysis exists it is already too late to give antitoxin Some recommend its use to those with positive throat cultures who seem to recover very quickly from their neuritis after receiving it Nasal feeding may be necessary in these patients because of faucial involvement Cardiac stimulants and artificial respiration may be necessary

Arsenic Polyneuropathy Intravenous injection of sodium thiosulfate (0 5 gm) in 10 c c of sterile water may hasten recovery Therapy is usually directed to the exfoliative dermatitis (for which a new and remarkably effective remedy called B A L has been developed) hepatitis and the aplastic blood picture

Lead Neuropathy The treatment is discussed on page 697

Cauda Equina Lesions The general practitioner should hardly be expected to make a differential diagnosis between a lesion of the lumbosacral cord itself and the roots which emerge from the spinal segments, but since lesions within the lower portion of the spinal canal produce flaccid paraplegias they will be discussed here If the lesion is of vascular or traumatic origin the symptoms have usually an acute onset and the history and examination

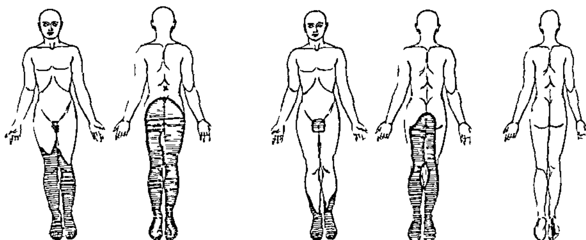


FIG 177 Anesthetic patterns in cauda equina lesions X marks site of entry of bullet *C demonstrates* an incomplete right sided lesion with analgesia of the right foot

A B C

FIG 178 A Saddle anesthesia The ruled area represents the sensory distribution of S_3 S_4 and part of S_5 B Ruled area represents the sensory distribution of S S and S_3 C *Right* leg stippling represents the radicular sensory distribution of L_3 L_4 and L_5 The diagonal striping represents the sensory distribution of S_1 S_2 and S_3 The left leg illustrates the sensory distribution of L_1 and L_2

will usually permit the correct diagnosis to be made without much difficulty This is not the case when the origin is a neoplasm of the cord or causal roots or a neuritis of the latter the symptoms are then slow in developing *The most common causes of cauda equina lesions are* fractures dislocations stab or gunshot wounds of the lumbar and sacral spine tumors either intraspinal or extra spinal in origin and inflammations usually tuberculous syphilitic or non specific

Symptoms The symptoms consist of either a slow or rapidly developing flaccid paraplegic syndrome with an associated sensory loss that sooner or later becomes segmental in distribution a tendency to genital and sphincter disturbances and decubitus Pain is the most prominent symptom It is usually localized to

symptoms will be absent but there will be saddle anesthesia '

7 If only the coccygeal root is involved there will be paralysis of the levator ani

Aids to Diagnosis The cerebrospinal fluid may show the changes described for spinal cord tumor If block exists expert aid may be necessary for a *lipiodol injection* and the correct interpretation of the subsequent roentgen study *Lumbar puncture* should be done as low as possible preferably through the fifth lumbar interspace Punctures made at higher levels may be above the lesion and therefore useless

The diagnosis may be very difficult and it often requires the aid of specialists It has been stressed by Joughin (9) that the general practitioner by close observation of obstinate

TABLE LVII

Differential of Cauda Equina and Conus Medullaris Lesions

Cauda Equina Lesion	Conus Medullaris Lesions
Bladder and rectal disturbances occur early and are severe	Absent or late—and then only when lowest sacral roots are involved
Saddle anesthesia is characteristic	Saddle anesthesia
Almost always bilateral	Asymmetrical or unilateral for a long period
Impairment of all forms of sensation	Sensation may be dissociated
Knee and ankle jerks absent	Only the ankle jerk absent and not in all cases
Flaccid paralysis of legs and feet	Trophic disturbances more common
Prognosis for recovery is fairly good	Hopeless prognosis

the lumbar region and down the back or front of one leg it usually follows the course of the roots and sometimes is confused with sciatica and so treated With the passing of time additional manifestations suggest a central lesion within the spinal canal They are

1 The pain is bilateral—suggestive of a central lesion
2 The knee jerk is diminished or absent—always present in the usual cas of sciatica
3 Paralysis of the bladder and rectum with incontinence
4 Atrophy of the anterior group of thigh muscles (not supplied by the sciatic nerve or its branches)
5 Sensory loss in areas corresponding to lumbar and sacral dermatomes
6 If the lesion is high in the cauda bladder

and atypical cases of lumbago and sciatica may often diagnose an oncoming flaccid paraplegia of central origin before it is complete

Treatment The treatment is surgical It consists of *laminectomy* followed when possible by the removal of growths In cases of trauma suture of the nerves may be necessary Careful attention should be paid to bladder function

Landry s Paralysis (Landry's Syndrome) Landry s syndrome which is also called acute ascending paralysis is usually fatal It is characterized by a flaccid paralysis of the lower limbs gradually ascending to involve the arms the bulbar and respiratory muscles and the cardiac and respiratory centers The cause is not known but it may be some form of toxic infection The disease may come on spontaneously or follow a general infectious dis

ease, some cases have been associated with a dietary deficiency There is nothing characteristic to be found in the spinal fluid The *diagnosis* offers no difficulty in view of the striking motor loss, the rapid ascent of the paralysis, and the absence of sensory symptoms While the disease is generally fatal in from a few days to a week occasionally the paralysis does not involve the bulb, and the patient recovers

Treatment There is no specific treatment Good nursing care and lumbar puncture with careful attention to the patient if in respiratory paralysis (then a respirator will be necessary) are about all that can be done If the patient is going to recover it will be noticed that the paralysis recedes in the reverse order of its progress The patient will require a long period of rest in bed, with massage and galvanism Recovery may require from two to three years

Pseudo Flaccid Paraplegias

Tabes Dorsalis *This is a sensory and not a* motor disorder It chiefly affects the sensory neurones being largely confined to the posterior nerve roots and the posterior columns of the cord Nevertheless, the patients show disturbances of gait, absent tendon reflexes *muscular hypotonus and sometimes, muscular* atrophy The disease in many instances also implicates the cranial nerves and thus provides valuable confirmatory clinical signs Many patients either have no knowledge of or deny a *previous syphilitic infection they have had no* secondary manifestations and many do not have Argyll Robertson pupils The course is usually progressive but may at any time become stationary The first stage is characterized by *stabbing lighting shooting pains* in the lower extremities due to root irritation There may also be *girdle pains* Other common sensations are a feeling of *walking on air or on a thick carpet* which is due *to anesthesia of the soles of the feet When the pains are slight* and before ataxia has developed it is not uncommon for patients to be treated for years as cases of rheumatism or neuritis If the root symptoms manifest themselves later as gastric crises they may be operated upon unnecessarily Interference with the vesical and rectal reflexes may result in *difficulty in beginning micturition* The following will assist in the diagnosis

1 Argyll Robertson pupil
2 Pronounced loss of position sense
3 Insensibility to pressure on the nerve trunks
4 Precipitous urination, difficulty in starting stream and sexual impotence
5 Ataxia
6 Lightning pains, girdle pains and, in some cases a cuirass shaped distribution of sensory loss over the chest
7 Absent knee and ankle jerks
8 Romberg sign positive
9 Positive blood and/or spinal Wassermann (In inactive and treated cases both blood and spinal fluid Wassermann may be negative, and other spinal fluid signs may be equivocal)

Treatment This is discussed on page 409–410

Conversion Hysteria (Hysteric Paraplegia) Hysteria may simulate organic paralysis or a compression syndrome A careful history and *physical examination should establish the diagnosis* The following may assist in arriving at the diagnosis

1 The reflexes are normal or exaggerated it is that which exists in many nervous individuals and it is also present in the non *paralyzed extremities* A false ankle clonus may exist which disappears when the leg is flexed at the knee and supported so that the muscles of the leg are relaxed
2 There is no atrophy except that which *may result from long disuse*
3 No true reaction of degeneration found
4 Motor power may be normal when recumbent yet the patient can barely stand He may run or dance and yet can walk *only with great effort*
5 Hemianesthesia is common but very seldom does the patient burn or cut the anesthetic skin
6 *There is no correlation between the distribution of the sensory* loss and any known anatomical distribution See figure 169
7 When the compression syndrome is simulated the pain and tenderness are general and not localized to the spine there is no deformity Babinski sign nor sphincteric disturbances

8 There may be an unstable and neurotic background in the family history

Muscular Dystrophy This disease is often familial or hereditary It usually begins in early childhood and may affect members of the same family Boys are afflicted more often than girls The clinical manifestations are difficulty in walking which is characterized by a waddling gait and in climbing stairs Atrophy of muscles usually appears around the shoulder or pelvic girdle and occasionally the back muscles are severely affected early in the disease The erector spinae muscles are affected early with a resultant compensatory lumbar lordosis and pot belly There is weakness of the lumbar muscles and both flexors and extensors of the hip and extensors of the leg on the thigh The muscular atrophy may be masked by the deposition of subcutaneous fat which results in pseudohypertrophy There is later atrophy of all weak muscles The *reflexes* are decreased and there is no reaction of degeneration The patient often cannot bend forward and raises himself from the dorsal recumbent position in a characteristic manner first turning over on to all fours he then grasps his legs and appears to ' climb up them into the upright position Sensation is not impaired The finding of large quantities of creatinine in the urine is of diagnostic importance

Treatment In view of the progressive nature of the disease operative measures are useless and not advised The patient should avoid any exertion Massage and electricity are of doubtful benefit There has been some success reported from the use of large amounts of *glycine* The dose recommended is 15 grams daily Other measures advised but which give little promise are *ephedrine sulfate* 25 mg two or three times a day *pancreatic extract* by mouth daily intravenous glucose injections *vitamin E* and a *high protein* diet beef extract and 10 grams of gelatin daily Orthopedic appliances are of only temporary value

Friedrich s Ataxia This disease is also familial and often affects several members of the same family The disease usually attacks boys in the period between 6 years and to the age of puberty There is a *progressive ataxia* of the legs and later of the arms Six to twelve years are required for the complete development of the disease There is a staggering gait and the patient walks on a wide base The ataxia is not sensory , nor is it affected by position or by closing the eyes As the disease progresses the following appear *hypotonia, decreased tendon reflexes, dysmetria adiadokoinesis nystagmus slow ataxic speech involuntary movements of the face* shoulders toes and fingers *Club foot* or extreme arching of the foot develops The *abdominal reflexes* are lost and a *bilateral Babinski* sign can be elicited The mental faculties are unaffected There is no known treatment

Peroneal Muscular Atrophy This disease is more common in males and begins early in life It may occur in more than one member of a family and rarely in several generations of the same family It begins in the small muscles of the feet and extends to the hands It never appears to progress beyond the peripheral part of the limbs Atrophy appears initially in the peroneal group of muscles and the extensor longus digitorum Steppage gait and foot drop follow and pes equinus varus or equinovarus may develop The atrophy may proceed to the point where the condition called *stork legs* is apparent There is no atrophy in the proximal parts of the limbs The paralysis is not absolute The knee and ankle jerks are absent and electrical changes occur up to an incomplete R D Fibrillary twitchings of atrophied muscles are not rare There is diminution of all forms of sensation in the distal parts of the limbs The disease is slowly progressive but it may not necessarily shorten the life of the patient It may remain stationary and show long remissions

Treatment The treatment is symptomatic Straps sewn on the soles of the shoes to support the foot may be of great comfort to the patient

Infantile Atrophies There are two common types Both are caused by degeneration of the anterior horn cells of the spinal cord and sometimes of the nuclei of the cranial nerves

Amyatonia Congenita This condition is often present at birth or soon after It is not familial There is extreme hypotonicity of the muscles which renders them virtually useless the child being unable to maintain any posture to raise his head to sit or to stand The

muscles do not respond to the faradic current The *reflexes* are absent There is no local atrophy nor reaction of degeneration There may be periods of remission and in some cases, there is a progressive tendency toward recovery without any treatment, but only rarely does complete recovery take place There is no treatment of value

Progressive Spinal Muscular Atrophy (Werdnig Hoffman Type) This is a familial type of muscular atrophy occurring in early childhood The atrophy is symmetrical and involves the shoulders, back muscles, hips, and extremities There is progressive loss of power in the limbs and, eventually, complete flaccid paralysis The *reflexes* are lost and the reaction of degeneration appears Death results in from two to five years Treatment is valueless in controlling the disease

Other Muscular Disorders

Myotonia Congenita—Thomsen's Disease This is a hereditary muscular disorder characterized by a marked increase in muscular tone and irritability, and slowness of relaxation following voluntary movements or electrical stimulation The exact nature of the disease is not known it may be a disease of the myoneural junction It occurs more frequently in males than in females and is usually first noticed at or shortly before puberty After shaking hands the patient is unable to relax his grasp for a few seconds On walking, a brief period is required to properly relax the muscles antagonistic to those which actually move the limbs forward Once started, however the patient walks in a normal fashion The symptoms of myotonia are precipitated or aggravated by emotion or cold and relieved by heat There is no atrophy the reflexes are unchanged and sensation is not involved The length of the patient s life is not affected

Treatment This consists of massage warm baths or removal to a warm climate *Quinine sulfate* or *dihydrochloride* 0 3 gm (5 gr) three times daily has a relaxing effect on the contracted muscles Prostigmine makes the condition worse

Myotonia Atrophica A somewhat similar but rare condition There is atrophy of the temporal and masseter muscles of the muscles of the hands of the quadriceps and of the muscles below the knee The sternomastoids are usually the most severely affected The face has been described as 'hatchet like' and the neck as "pole like" The disease is frequently complicated by cataract Not infrequently there are impotence, testicular atrophy, baldness, disturbances of speech and loss of the knee jerks Pulmonary tuberculosis is common *Quinine* is of some assistance

Family Periodic Paralysis This is a rare hereditary disease, the probable cause being an inborn metabolic error resulting in potassium deficiency The muscles are attacked periodically and a flaccid paralysis results which develops abruptly and lasts for a few hours to a number of days During the acute stage death may result from respiratory paralysis The muscles of the lower extremities are usually involved first followed by paralysis of the arms The muscles of the abdomen are often affected The deep reflexes and all electrical response are lost There is no sensory disturbance The attacks may come on while the patient is asleep Once recovery starts, it proceeds rapidly *Hysteria* is sometimes confused with this disease but the changes in the electrical reactions and the reflexes are never abnormal in hysteria

Treatment If *potassium chloride* is given to a patient during an attack, recovery may ensue within the hour and not infrequently in from ten to fifteen minutes Potassium chloride is given by mouth in doses of from 2 to 5 grams in water, or in the form of potassium citrate 1 to 3 grams The dose may be repeated in a few hours Some patients have prodromal symptoms of hunger thirst, sweating diminution of salivation, and a feeling of swelling or stiffness in the limbs before an attack When this is known the attack may be aborted by the administration of some form of potassium

Myasthenia Gravis Myasthenia gravis is a disease whose outstanding feature is an excessive fatigue of the muscles due to a disorder of function at the myoneural junction *It is* usually a disease of middle life appearing in the fourth and fifth decades but it has been seen in patients as young as eight and ten years of age Sensory symptoms atrophy, fibrillation reaction of degeneration and

sphincter disturbances are absent The onset may be acute with ptosis or dysarthria At tacks may be precipitated by pregnancy or some psychic disorder Rarely a persistent thymus gland is found The disease progresses slowly by relapses and remissions Because certain muscle groups are affected the disease falls into three groups In one group the ocular muscles are affected giving rise to ptosis diplopia or both A second group involves the muscles of the face and throat, causing dysphagia, dysarthria and weakness of the jaw A third group is that of general muscular weakness, the neck muscles being more involved than any of the others

Diagnosis Fatigue increases all kinds of muscular weakness but only in myasthenia gravis is actual paralysis induced by use of the muscles The patient complains not of feel ing tired or that his muscles ache but rather of extreme weakness after exercise When severe weakness is present upon awakening and may persist for from days to weeks at a time It is extremely unusual for the muscles of the limbs to be involved without ptosis, or weakness of the ocular muscles or masseters The most convincing *test for myasthenic paraly sis* is therefore either to have the patient look upward at the examiner s finger steadily for one minute this should induce ptosis if the levator is affected and sometimes strabismus Another equally valuable test is to have the patient raise the lower jaw every two seconds against resistance applied by the examiner If the masseters are affected great weakness will be felt after ten repetitions In the upper limbs a similar muscular failure with use will be elicited by making the patient abduct the arm at the shoulder or extend the elbow re peatedly against resistance *Prostigmine* may be used as a therapeutic test Weakness having been elicited by a suitable test the patient is given 1 mgm of prostigmine subcu taneously In from 20 to 40 minutes the weakness should have largely disappeared if it is due to myasthenia gravis Occasionally the *myasthenic reaction of Jolly* can be demon strated This consists of a rapid failure in muscular response on repeated stimulation with the faradic current *Quinine* may be used as a diagnostic test If its administra tion aggravates the myasthenia the diagnosis is certain The diagnosis is often mistaken for psychoneurosis neurosyphilis or cerebral vascular disease

Treatment Rest and the avoidance of any exhaustion are essential The patient should eat slowly and speak little Attention should be paid to his diet which should be adequate and nourishing *Deep roentgen therapy* of the thy mus gland may be tried Eaton (10), after re view of the literature, concludes that in many cases the relation of myasthenia gravis to thy mic abnormalities has been established He suggests that roentgen studies of the chest including lateral views be made in every case in order to determine whether the thymus is enlarged Harvey and his co workers (11) have studied the state of neuro-muscular trans mission and the effects upon it of prostigmine and acetylcholine in 5 patients with severe myasthenia gravis 5 months after total extirpa tion of the thymus gland Three of the five patients have shown a marked degree of clinical improvement which developed concurrently with a reversion of neuromuscular function toward the normal They suggest that such changes after thymectomy indicate an increase in the transmitter substances available at the neuromuscular junction *Prostigmine* is now used orally in the treatment of myasthenia gravis Two 15 mg tablets up to a total of twelve per day given orally are effective Large doses of potassium chloride (2–3 gm) may be administered either simultaneously or alternately with the prostigmine Intramuscular injections of *prostigmine methylsulfate* may carry a patient through a respiratory crisis It is given in a dose of 10 to 15 mg *Atropine* gr $\frac{1}{150}$ may be added to counteract any distressing side effects of prostigmine especially excessive peristalsis

Disorders of the Cranial Nerves

TRIGEMINAL AND GLOSSOPHARYNGEAL NEURALGIA

Trigeminal neuralgia or tic doloreaux is the most common form of neuralgia The cause is unknown It is nearly always unilateral and is more common on the right side One or all three divisions of the trigeminal nerve (see figure 173) may be involved The pain is one of the most excruciating of all pains to

which mankind is heir, and not a few of its victims have committed suicide It occurs usually in middle life and is more common in women Most patients have a "trigger zone" located over the supra and infra orbital notches over the mental foramen, the gums and in front of the ear The onset is sudden and dramatic and often stuns the patient by its intensity He is afraid to move, open his mouth breathe, talk eat, wash his face or brush his teeth The onset is usually brought on by a chill laughing stroking the face, exposure to cold air or exertion The patient is free from pain between attacks but lives in dread awaiting their recurrence There is rarely only one attack they are usually repeated at short intervals

Diagnosis

The dramatic onset and a glance at the patient point to the diagnosis In Sluder s *sphenopalatine neuralgia* the pain is usually localed under the zygoma, there are no trigger zones and the pain is steady Cushing and Frazier have cast doubt on this syndrome Immediate relief is said to follow the application of novocaine to the nasal mucous membrane or its injection into the ganglion, and is regarded as diagnostic

Glossopharyngeal Neuralgia should not cause any difficulty in diagnosis The pain radiates from the pharynx or the tonsil The patient says the pain is in his throat and points to an area below the angle of the jaw it radiates to the ear Swallowing may initiate an attack

Treatment

Medical treatment can offer little Even morphine will not relieve the pain The face *should not be touched* *Give warm or tepid* water to drink instead of cold If the patient is afraid to eat or drink he should be given fluids intravenously or by hypodermoclysis *Trichlorethylene* 20 minims inhaled three times daily from a handkerchief may relieve the pain Focal infections should be sought and eliminated but this does not mean the removal of all the patient's teeth on a mere suspicion of their being responsible *Short wave* and 10 000 units of *thiamine chloride* daily for a week have been suggested but the results are questionable *The best treatment is surgical* excellent results having been achieved by the gasserian ganglion operation as perfected by Cushing and Frazier The sensory roots are severed proximal to the ganglion or in some cases, a substantial resection is performed thus avoiding post-operative keratitis The eye on the operated side should be covered in order to prevent drying and trauma of the cornea This may be effected by air tight goggles, by sealing a watch crystal tightly over the orbital rim with adhesive plaster, or, when a more severe ulcer has developed or seems imminent the lids may be stitched together for *a period of a few days to a few weeks*

Treatment of Glossopharyngeal Neuralgia. Treatment consists in section of the ninth cranial nerve intracranially Though the actual section is a simple operation, it requires craniotomy

MENIERE'S DISEASE

This syndrome is an affection of the 8th *cranial nerve* *The typical attack* is a sudden violent vertigo frequently of such intensity as to cause the patient to fall as though he had been knocked down The attack is accompanied by nausea vomiting, pallor, nystagmus diplopia and diarrhea The patient usually lies on one side and is careful not to move his head suddenly There may be tinnitus and deafness The paroxysm lasts from several minutes to days *it may come on daily* Occasionally the attacks are nocturnal The cause is not known Syndromes not unlike that of Meniere s disease are seen in *hysteria* anxiety and traumatic neuroses, in tumors at the cerebello-pontine angle and in vascular anomalies about the auditory nerve The original clinical syndrome was characterized by an acute hemorrhagic extravasation into the labyrinth

Treatment

The Furstenberg diet which limits sodium salts and gives ammonium chloride is said by some workers to be of value Talbott and Brown advise a diet of normal sodium content with the addition of 6 to 10 grams daily of potassium chloride in aqueous solution *Cure has not been claimed* but nearly all the 40 patients so treated by Talbott and Brown were relieved and able to live relatively normal lives

Low Sodium Diet This implies the avoidance of the following foods

Salt meats and fish bread, crackers, and butter prepared with salt

Carrots	Clams
Cowpeas	Caviar
Cheese	Endive
Condensed milk	Raisins
Olives	Spinach
Oysters	

Limited use of the following is allowed (twice weekly)

Lima beans	Beets
Cauliflower	Celery
Dry coconut	Figs
Limes	Kohlrabi
Mustards	Pumpkin
Watercress	Rutabagas
Buttermilk	Cantaloupe
Chard	Dates
Dry currants	Horseradish
Peanuts	Peaches
Strawberries	Turnips
Radishes	

Nicotinic acid and *thiamine chloride* given together are said to be valuable when vasospasm is suspected Horton of the Mayo Clinic has reported good results using *histamine* intravenously 1 mg of the base is added to 250 c c of normal saline solution and given intravenously over a period of from one to one and a half hours For maintenance Horton suggests 0 1 to 0 2 mg of the histamine base subcutaneously from two to four times a week

Surgery It is conceded that the best results are obtained by section of the vestibular division of the acoustic nerve Dandy has reported 401 operations with only one death, which was from meningiti It has been found that this operation controls the seizures without affecting hearing

BELL S PALSY

This is a common condition and is marked by paralysis of all the facial muscles on one side of the face with the exception of the levator of the eyelid The most common cause is compression of the facial nerve where it passes through the Fallopian canal Edema results and is followed by degeneration of the nerve In other instances exposure to cold may be the exciting cause It may occur in the course of an infectious disease such as diphtheria mumps diabetes otitis media and caries of the petrous portion of the temporal bone In hypertension it may result from hemorrhage into the facial canal from the petrosal or stylomastoid artery Any disease of the pons may cause facial palsy but there will usually be signs of the involvement of adjacent structures i e pyramidal tract descending sensory trigeminal root or the sixth nucleus Facial diplegia may be due to alcoholic polyneuritis tetanus and myasthenia gravis

Signs and Symptoms

The facial expression in Bell s palsy is characteristic The face appears flattened out, the corner of the mouth droops the palpebral fissure is widened the lid cannot be closed, the forehead cannot be wrinkled nor can the patient whistle or blow out his cheek There is lacrimation and blinking is impossible on the affected side and on this side the tongue may appear narrower and food may dribble from the mouth

Course

In an ordinary facial neuritis the course is fairly rapid with complete paralysis in a few days Mild paralysis with few or no electric changes may last for from two to several weeks though in stubborn cases it may persist for six months or more Faradic or galvanic impairment of mild degree portends an early recovery, but the complete reaction of degeneration suggests either a prolonged course or that the condition will not improve

Diagnosis

If the lesion is above the 7th nucleus paralysis is incomplete and the muscles of the eyelid and forehead are unaffected *If the lesion is in the nucleus or peripheral to it* there is complete facial paralysis *If the nerve is affected during its course with the chorda tympani* taste is lost over the anterior two thirds of the tongue

Treatment

Massage electric stimulation and roentgen therapy have been used in certain cases with benefit The eye should be protected from drying and frequent washings with boric acid

are advised In the great majority of cases of uncomplicated Bell's palsy, recovery occurs without treatment Anastomosis with the hypoglossal or accessory nerve has been tried with occasional success when spontaneous recovery did not occur Adhesive tape can be used to keep the involved cheek from drooping Traumatic facial palsy and that following ear disease are likely to be permanent

SEASICKNESS

Seasickness is described here since it is undoubtedly related to the vestibular apparatus This syndrome has been widely discussed and with much diversity of opinion as to its cause, yet no treatment on a rational basis has been perfected It has been described as being due to the rolling and pitching of the ship and the unaccustomed stimulation of the receptors of the semicircular canals Predisposing causes are poor ventilation, unpleasant odors, constipation, migraine disturbances of orientation, vagotonia gastro intestinal disturbances the sight and sound of others who are sick and psychic impressions in apprehensive subjects even before the vessel sail

Abnormal conditions induced by unusual movements are not limited to man, horses dogs cattle, sheep and other animals become seasick It is stated that women and neurotic persons are more susceptible to seasickness Racial differences have been described In the writer's experience, Filipinos and Puerto Ricans appear to be very susceptible while negoes are relatively immune Deaf mutes and those in whom the vestibular apparatus is functionless do not suffer Children accustomed to spinning, infants and the aged are relatively immune

Seamen greatly dislike to admit that they become seasick since they may be ridiculed or even treated with contempt When forced to go to the ship s doctor they usually complain of other ailments ranging from low back pain to headache in the hope that they will be put on the sick list and allowed to remain in their bunks Keevil (35) calculated that only 0 023 per thousand able bodied seamen failed to acquire immunity and that only 0 014 per thousand suffered severe attacks These figures may account for the Navy s comparative lack of interest in seasickness

Treatment of Seasickness

It is generally agreed that measures conducive to good hygiene and health such as rest fresh air, exercise and a good but simple diet should be followed Cases of the so called postural or visceral type must remain in bed *Chloral* has been advocated either alone (Blackham (36) and Zorab (37) or in conjunction with bromides (Hill (38) and Keevil (35)) *Chlorbutanol* (chloretone) is the active ingredient used in Mothersill's seasick remedy It has been thought to be objectionable because of its anesthetic effect on the gastric mucosa, thus impairing both appetite and digestion (38) (39) Sensory depression can do harm in the vagotonic type of patient, and for this reason chlorobutanol or *barbiturates* are only advocated when sedation is clearly indicated The vagotonic type of reaction usually predominates among men and for this reason *atropine* is partially specific because of the frequency of vagotonia Schwab (40) stated that of many drugs tried it gave the best results Some investigators (40) (41) (42) (35) have found scopolamine effective while others preferred the tincture of belladonna or the total alkaloids The dosage advocated is *tincture of belladonna* 20 minims three times daily, or, grain one hundredth of *hyoscine hydrobromide* *Scopolamine with hyoscine* has been found effective for the relief of vomiting but not so effective for the relief of postural dizziness This combination is marketed as *Vasano* (Schering)—the tablets contain hyoscyamine 0 4 mg and scopolamine 0 1 mg The author has used *benzedrine sulfate* with excellent results (78 per cent complete relief of symptoms) (43) Hill (39) has recommended a prescription to be varied according to the type of patient as follows

	Vagotonics		Sympatheticotonics		Amphotonics	
Tincture of belladonna	Minims	15	Minims	5	Minims	10
Bromides	grains	40	grains	80	grains	60
Chloral hydrate	grains	15	grains	25	grains	0

In a later paper (44) he suggested the addition of benzedrine or belladonna except in the case of sympatheticotonia Ekerfors (45) recommends the combination of benzedrine chlorobutanol and papaverine

Remedies which have undergone comparative tests to date include

1 Hyoscine HBr, 0 65 mgm The dosage may be repeated in 8 hours
2 Royal Canadian Navy treatment Hyoscine HBr 0 32 mgm hyoscyamine HBr 0 87 mgm, niacin 150 mgm Half dose may be repeated in 8 hours
3 Army development type Atropine sulphate 0 32 mgm, hyoscine HBr 0 43 mgm sodium amytal 130 mgm Half dose may be repeated in 8 hours

The existing remedies are not effective in all cases but this should not detract from their usefulness for those who derive benefit from them Hyoscine alone, is the favored drug at the present time The routine use of seasickness remedies should be discouraged in those who follow the sea as a trade since those who cannot overcome susceptibility to motion sickness through habituation should not be dependent upon drugs to maintain physical efficiency Also while the side effects are slight their consequence upon continued administration is not yet sufficiently well understood to permit prediction of effects

Diseases of the Peripheral Nerves

BRACHIAL NEURITIS

In brachial neuritis the roots of trunks of the nerves are involved either primarily or secondarily The pain travels down the shoulder and arm along the course of the nerve and is usually increased by movement It is often aching in character and may disappear with sleep The nerve is tender Some of the cau es suggested are tennis playing piano playing (this is very dubious) and such diseases as gout rheumatism cachectic states diabetes and anemia In considering the *differential diagnosis* one should exclude subdeltoid and subacromial bursitis deltoid myositis and arthritis as well as brachial plexus injury and pressure upon the plexus by tumors or a cervical rib There may be referred pain from liver or gallbladder disease The lesion is usually unilateral and there may be trophic changes about the joints and fingers

Treatment

Rest and warmth over the affected part give definite relief Analgesic drugs are valuable and a mustard plaster over the brachial plexus will often bring much relief

INTERCOSTAL NEURITIS

This disease is not very common but is often diagnosed incorrectly It may occur in connection with pregnancy lactation and menstruation One must exclude *rib fractures, pleurodynia aneurysms, cord tumors* and *diseases* of the *heart stomach* and *liver* Referred pain from abdominal disease is a frequent source of confusion The pain follows the course of the nerve between the ribs to the front of the chest there may be pointed tenderness at the vertebral exit of the nerve as well as in the axillary and midsternal lines A special type (D3 to D6) called *mastodynia* in which pain and tenderness of the breast accompanied by hyperesthesia of the nipple are experienced *Treatment* is similar to that for other types of interstitial neuritis with rest warmth and analgesics, counter irritants, injection and even nerve section The *prognosis* is good

SCIATIC NEURITIS

The sciatic syndrome is not a true neuritis as a rule, but a referred pain Primary sciatic neuritis is rare and usually caused by poisoning with lead arsenic or alcohol or by syphilis The usual syndrome results from exposure infection, injury and strains of the lumbo sacro iliac region The pain may be caused by osteoarthritis of the lower spine herniation of an intervertebral disc or hypertrophy of the ligamentum flavum In many cases, no cause can be found The dominant symptom is severe pain both spontaneous and on pressure over the nerve trunk The pain is felt down the back of the leg along the lateral or medial border and it may jump from the thigh to the foot It is usually described as burning or stinging in character The pain is often worse at night Rest in bed gives comfort while sitting or walking aggravates it Relief may be gained by flexing the knee in the recumbent position The pain may be aggravated by coughing or sneezing which increases the intraspinal pressure Extending the knee with the hip flexed causes severe pain as this stretches the nerve The attacks may clear up in a few weeks or be prolonged for months Relapses are common There may be functional

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The Dejerine Klumpke Syndrome

This is the lower arm type of brachial plexus lesion The paralyzed muscles are those supplied by the ulnar nerve and part of those supplied by the median nerve The usual causes are fracture or dislocation of the head of the humerus violent traction during an attempted reduction sudden jerking of the arm upward or clutching something in an attempt to save a person from a fall It may occur in breech delivery when the arm is extended by the side of the after coming head

Signs and Symptoms

1 The small muscles of the hand are affected with a resultant claw hand and atrophy
2 Sensation lost in the ulnar region of hand
3 If the lesion is close to vertebral foramina the sympathetic rami are involved and *Horner s syndrome* will be present

Treatment

1 The treatment is the same as that for the upper arm type only the prognosis is not as favorable since operation is difficult and nerve repair is not always successful
2 If the roots are torn near the vertebral canal or as they leave the cord the outlook is hopeles

Long Thoracic Ner e

Causes of Involvement

1 Perforating wounds in supraclavicular fossa or axilla
2 Severe blows on the neck
3 Violent stretching on raising arm above head
4 Carrying heavy weights on the shoulder

Symptoms and Signs

1 The scapula cannot be fixed Winging is noted
2 Weight carrying is interfered with
3 Elevating arm above horizontal level is difficult
4 Prognosis fair in neuritis poor in trauma

Treatment Transplantation of a portion of the pectoralis major into the serratus anterior muscle may overcome some of the paralysis

Cervical Rib Syndrome

This is one of the causes of brachial plexus paralysis The first thoracic root may be compressed by a cervical rib and in some cases even by a normal first rib Supernumerary ribs are congenital they are not rare and occur more commonly in women They may be present without symptoms When there are symptoms they are usually bilateral, when unilateral they are generally on the right side

Signs and Symptoms

1 Pain or paresthesia in ulnar region of the forearm and hand
2 Weakness and atrophy of the small muscles of the hand
3 As condition progresses there is impaired touch pain and temperature sense
4 Radial pulse smaller or absent on the affected side especially when the arm is raised

Diagnosis

1 The rib may be demonstrated by roentgen study
2 Unequal radial pulse and isolated eighth cervical and first dorsal root symptoms
3 In some cases the rib may be palpated

Treatment

1 Removal of the rib or cutting the fibrous band which may be the cause of the syndrome
2 In some cases section of the scalenus anticus gives relief

Scalenus Anticus Syndrome

This syndrome may simulate the symptoms caused by a cervical rib In this case a tight scalenus muscle is pressing the subclavian artery against the brachial plexus The condition is congenital and the symptoms may not appear until adult life Point pressure upon the insertion of the muscle or dropping the shoulder and flexing the head to the opposite side causes pain to radiate down the arm or back of the neck and shoul er

Treatment [illegible] e muscle usually furnishes

scoliosis The ankle jerk may be absent, the gluteal fold obliterated, and sensory alterations in the course of the sciatic nerve on the affected side may appear

Treatment

Rest in bed, analgesic drugs, and heat applied along the course of the nerve give relief Radiant heat, diathermy, and gentle massage are beneficial Leg traction is advised by some When the disease is localized along the nerve root or high up in the sacral plexus epidural injection has given excellent results When the nerve trunk in the thigh is affected, the nerve itself may be injected usually at the sciatic notch If 1 c c of saline is injected and the patient feels pain in the foot 2 c c of 2 per cent novocaine are injected followed by 40 to 80 c c of normal saline Success with this treatment is reported in about half the cases Any foci of infection should be removed

PHRENIC NEURITIS

Causes of Involvement

1 Anterior poliomyelitis
2 Tumors
3 Landry s paralysis
4 Fractures of adjacent cervical vertebrae
5 Operative injury
6 Compression by aneurysm or mediastinal tumor
7 Gunshot or stab wounds of the neck
8 Infectious neuritis—diphtheria
9 Erb s obstetrical palsy

Symptoms and Signs

1 Dyspnea upon exertion difficulty in coughing and sneezing
2 Immobility of diaphragm on fluoroscopic study
3 Liver may lie higher up on involved side
4 Abdominal muscles cannot be protruded on expiration the abdomen is scaphoid in shape
5 Pneumonia may follow bilateral paralysis

Diagnosis

Fluoroscopic study is conclusive The nerve may be electrically tested in the neck between the sternomastoid and scalenus anticus and above the omohyoid

Treatment

The treatment consists of absolute rest

NERVES OF THE BRACHIAL PLEXUS

Details of the brachial plexus may be found in any test on anatomy It is important to be familiar with the primary trunks and the cords which arise from them *Trunk lesions* result in radicular syndromes *Cord lesions* give rise to lesions resembling peripheral nerve dysfunction Trunk lesions give rise to partial muscle paralysis and the loss of sensation follows the radicular, not the peripheral nerve distribution, they are found at the vertebral border high up in the supraclavicular fossa or near the scaleni muscles Cord lesions occur in the lower supraclavicular fossa or axilla

The Duchenne Erb Syndrome

This may be caused by wounds or tumors but it is most commonly the result of stretching or tearing of the trunk from traction on the head during obstetrical delivery It is the usual type of birth palsy The muscles chiefly affected are the deltoid, biceps brachialis anticus and supinator longus In addition there may be some involvement of the flexors of the wrist and fingers

Signs and Symptoms

1 The arm hangs limp and cannot be abducted or rotated outward
2 Elbow flexion is impossible
3 Sensory impairment is confined to the outside of the arm
4 R D present and atrophy marked
5 There may be spontaneous recovery

Treatment

1 Prevent overstretching by use of splints
2 Massage passive movement and galvanism are useful
3 Nerves caught in scar tissue are sometimes successfully treated by operation
4 If the roots are torn near the vertebral canal or out of the cord the outlook is hopeless
5 Nerve anastomoses rarely succeed

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Signs and Symptoms

1. Pain or paresthesia in ulnar region of the forearm and hand
2. Weakness and atrophy of the small muscles of the hand
3. As condition progresses there is impaired touch pain and temperature sense
4. Radial pulse smaller or absent on the affected side especially when the arm is raised

Diagnosis

1. The rib may be demonstrated by roentgen study
2. Unequal radial pulse and isolated eighth cervical and first dorsal root symptoms
3. In some cases the rib may be palpated

Treatment

1. Removal of the rib or cutting the fibrous band which may be the cause of the syndrome
2. In some cases section of the scalenus anticus gives relief

Scalenus Anticus Syndrome

This syndrome may simulate the symptoms caused by a cervical rib In this case a tight scalenus muscle is pressing the subclavian artery against the brachial plexus The con dition is congenital and the symptoms may not appear until adult life Point pressure upon the insertion of the muscle or dropping the shoulder and flexing the head to the opposite side causes pain to radiate down the arm or back of the neck and shoulder

Treatment Section of the scalene muscle usually furnishes relief

Circumflex Nerve

Mode of Injury

1 Severe downward blow on the shoulder
2 Fractures or dislocations of head of humerus
3 Pressure on the shoulder from deep sleep, or from laying on the side for long periods (miners)
4 Stab and gunshot wounds
5 Lead and carbon monoxide poisoning, infectious diseases
6 Neuritis secondary to inflammation of joint

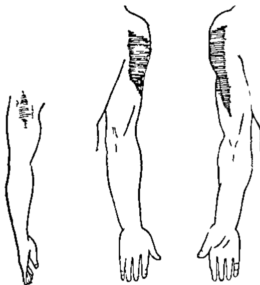


Fig 179 Sensory Topography of the Circumflex Nerve (Cutaneous) of the Shoulder

Signs and Symptoms

1 Paralysis of deltoid and teres minor muscle
2 Abduction of the arm is impossible
3 Shoulder joint relaxed and there is loss of round contour, it becomes angular
4 Objective sensory disturbance in a small oval area at tip of shoulder and upper external surface of the arm

Treatment The treatment is like that of other nerve palsies An abduction shoulder splint may be needed to prevent overstretching of the deltoid muscle

Musculocutaneous Nerve

Mode of Injury This nerve is seldom injured alone, but usually with the radial nerve in lesions of the humerus Aneurysm of the axillary artery, severe blows to or compression of the arm and direct wounds are other causes of injury

Signs and Symptoms

1 The biceps jerk is lost
2 Anesthesia on outer and anterior surfaces of the forearm The sensory loss is ill defined posteriorly, as there is considerable overlapping with the musculospiral nerve

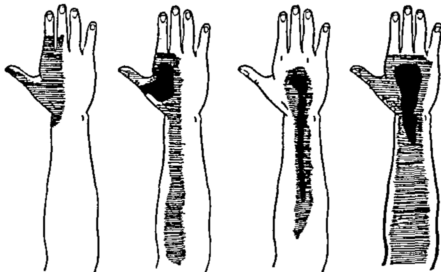


Fig 180 Patterns of Sensory Loss from Lesions of the Radial Nerve Solid Black Indicates Loss of Pain Touch and Temperature

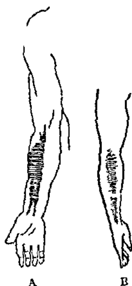


FIG 181 A Sensory area of the musculocutaneous nerve B Cutaneous anesthesia in complete section of the musculocutaneous nerve

3 Supination is weak owing to los of biceps action
4 Injury to the nerve in the upper third of the arm results in paralysis of the muscles supplied which are the chief flexors of the forearm Flexion is still pos ible through the action of the supinator longus If the forearm is supinated there is paralysis of flexion

Radial Nerve

Mode of Injury This is the most likely of all peripheral nerves to be injured It may be pressed on by a crutch or when the arm is hung over a chair or bench Direct trauma compression by a callus lying heavily on the arm while asleep or while anesthetized on the operating table fracture of the humerus or dislocation in the axilla Lead neuritis or an Esmarch bandage may lead to paralysis

Signs and Symptoms Paralysis of the radial nerve results in the following symptoms
1 Inability to extend the (triceps) elbow
2 Inability to extend the wrist
3 Inability to extend the fingers
4 Inability to extend the thumb
5 Weakening of elbow flexion as a result of the paralysis of the supinator longus
6 Weakening of supination

A *Lesion of Nerve High Up (Crutch Palsy)*
1 Paralysis of extension of elbow
2 Wrist drop
3 Weakness of supination and flexion of the forearm
4 Sensory loss in the dorsum of the hand
5 Triceps reflex will be absent

B *Injury Above Point of Origin of Nerve to the Supinator Longus*
1 Same picture as described above except that the triceps and triceps reflex are spared
2 If the external cutaneous branch is spared there will be no sensory loss This is the most common site of injury to the nerve

C *Injury Below the Supinator Longus Nerve*
1 Wrist drop If the nerve to the extensor carpi radialis longior is spared some extension of the wrist will be possible on the radial side
2 There is no sensory loss

D *In the Forearm*
1 A little below the elbow a wound of the posterior interosseous will spare the nerve to the short radial extensor and extension of the wrist on the radial side will be intact
2 Paralysis of ulnar extensor of the wrist, extensors of the fingers, and extensors of the thumb
3 There is no sensory loss

Treatment Splinting galvanism and massage are the important methods of treatment It is important to keep the fingers and wrist extended by a splint until recovery has taken place In many ca es of injury operations upon the nerve is required

Median Nerve

The median nerve is well protected and is not often injured It may be affected in the axilla or the forearm but, generally, the lesion is in the palmar surface of the wrist It is often the site of causalgia and may be damaged by prolonged occupational pressure

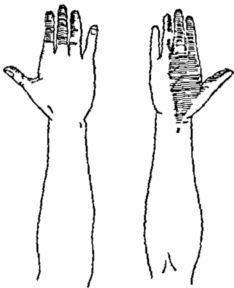
A *Complete Lesion*
1 Paralysis of the flexors of the wrist terminal phalanx of thumb and

phalanges of index finger with weakness but not complete paralysis of flexion of the other fingers

2 Paralysis of the muscles of grip
3 Atrophy of the thenar eminence
4 Pronation is impossible except passively from weight of arm
5 Region of sensory loss is less than the area of cutaneous distribution See figure 182

B *Injury in Lower Forearm and Wrist*

Only the muscles of the thumb may be affected The sensory loss is as described before



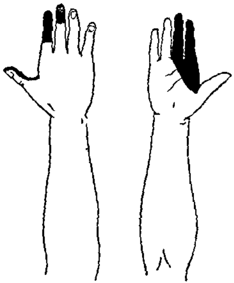


FIG 182 Patterns of Sensory Loss from Injuries to the Median Nerve

After complete division of the median nerve there is no characteristic deformity of the hand Many of the movements which have been lost are performed by other muscles The diagnosis is suggested by the loss of flexion of the terminal phalanx of the thumb, and the loss of opposition of the thumb so that it cannot touch the tips of the other fingers

C *Combined Ulnar and Median Nerves*

Combined involvement is common because of the close association of these nerves in the upper arm

Signs and Symptoms

1 Complete paralysis of the muscles supplied by both nerves
2 Loss of flexion of the wrist and fingers
3 Loss of pronation of the forearm
4 All the small muscles of the thenar and hypothenar eminences and the interossei and lumbricals are atrophied
5 There is marked wasting of the palm
6 Adduction and abduction of the fingers and opposition of thumb to fingers are lost
7 The sensory loss is that of the combined sensory distribution of the two nerves

Treatment Operation is not wholly successful The prognosis is not as good as in radial nerve injuries Motion may return but

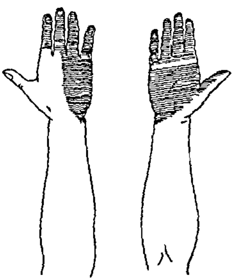


FIG 183 Combined Paralysis of the Ulnar and Median Nerve

sensation is seldom normal even after a few years of treatment

Ulnar Nerve

Mode of Injury

1 Fracture of the inner condyle of the humerus
2 Dislocations of the elbow joint
3 Ulnar neuroma
4 Leprosy
5 Syphilis

Signs and Symptoms

1 Loss or impairment of adduction of fingers
2 Loss of extension of distal phalanges and flexion of the proximal phalanges resulting in 'claw hand'
3 Hand deviates to radial side on flexion of the wrist
4 Atrophy of small muscles of the hand, with deep 'grooving' of interosseous spaces
5 Sensory loss localized to little finger, area over hypothenar eminence, and one half of the little finger

Prognosis Contractures may result and the paralysis is rarely completely recovered from

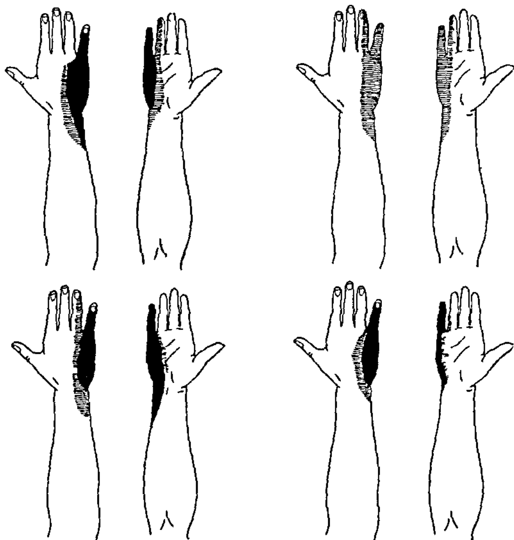


Fig 184 Patterns of Sensory Loss from Lesions of the Ulnar Nerve

Treatment The treatment is that for lesions of other peripheral nerves

NERVES OF THE LOWER EXTREMITY

Femoral Nerve (Anterior Crural)

Mode of Injury

1. Neuritis may occur in diabetes
2. Fracture of upper end of femur or the pelvis
3. Gunshot or stab wounds
4. Pelvic tumors
5. Psoas abscess
6. Injury during labor, particularly when forceps are used
7. Aneurysm of deep femoral artery is a rare cause

Signs and Symptoms

1. If there is complete division, the chief symptom is loss of extension of the leg (quadriceps extensor) The patellar reflex is lost
2. Walking forward is difficult, for, owing to the failure of the extensors the leg gives way at the knee during flexion Walking backwards is much easier
3. If the nerve is injured high up in the pelvis owing to paralysis of the psoas, the thigh cannot be flexed upon the trunk
4. Sensory Loss Cutaneous sensibility is lost over the antero internal aspect of the thigh, and the inner aspect of the knee, leg and foot
5. Atrophy of the quadriceps muscle

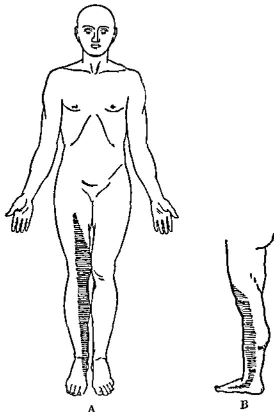


Fig 185 A Cutaneous sensory distribution of the femoral (anterior crural) nerve B Cutaneous sensory distribution of the internal saphenous nerve

Obturator Nerve

Mode of Injury Injury usually occurs during difficult labor, but it may result from dislocation of the hip

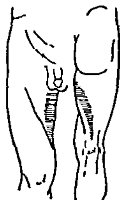


Fig 186 Cutaneous Sensory Distribution of the Obturator Nerve

Signs and Symptoms

1. Loss of power in adduction of the thigh
2. Outward rotation of the thigh is impaired
3. Sensory loss is minimal owing to overlapping of adjacent cutaneous nerves

Lateral Femoral Cutaneous Nerve

This sensory nerve supplies the upper and outer portion of the thigh It is frequently the site of paresthesias and neuralgia (meralgia paresthetica) The causes are believed to be (1) neuritis (2) obesity (3) spondylitis (4) flatfeet (5) angulation of the nerve as it leaves the pelvis and (6) pressure of the fascia

Signs and Symptoms

1. May only be present when patient is standing, owing to a pendulous abdomen

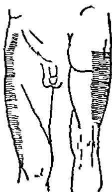


Fig 187 Sensory Distribution of the Lateral Femoral Cutaneous Nerve

2 Pain numbness and tingling on front and outer side of the thigh
3 Usually occurs in middle aged obese persons

Treatment The treatment consists of abdominal supports freeing the nerve from its fibrous tissue resection in intractable cases, and rest

Sciatic Nerve

Mode of Injury

1 Gunshot or stab wounds
2 Fractures and dislocations of the hip
3 Deep injections into the hip
4 Alcoholic polyneuritis
5 Neuritis from osteoarthritis of the spine or sacroiliac joint
6 Tumors in the pelvis
7 Pressure of the head in dystocia or from the application of forceps
8 Fracture of the pelvis

Signs and Symptoms

1 In complete paralysis flexion of the leg is lost
2 Since the nerve to the semi membranous and tendinosus is given off at a high level, paralysis of flexion is rare but there may be weakness of some of the flexors of the leg
3 The foot dangles when the patient stands
4 Steppage gait is present—to overcome the foot drop
5 All muscles below the knee are paralyzed
6 Running is impossible
7 Reflexes
   a Knee jerk is present
   b Ankle jerk and plantar reflex are absent
8 Edema and discoloration of the foot are common The edema may conceal muscle atrophy There may be plantar hyperkeratosis
9 In complete lesions sensation is lost over the entire foot with the exception of the inner border of the arch and the inner malleolus the loss extends over the outer side of the leg to the knee As a result of ankylosis plantar injury is common and owing to vasomotor changes, healing is very slow

Common Peroneal Nerve

Mode of Injury

1 From pressure or damage at knee level either directly, or from prolonged kneeling or crouching at work
2 Lead neuritis
3 Protracted labor

Signs and Symptoms

1 Foot drop and pes equinovarus
2 Steppage gait
3 Loss of extension or dorsiflexion of the proximal phalanges
4 Loss of abduction of the foot

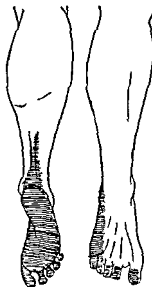


Fig 188 Sensory Cutaneous Distribution of the Tibial (Internal Popliteal) Nerve

5 Cutaneous sensibility is destroyed over the dorsum of the foot and anterior and outer surfaces of the leg The dorsum of the foot is involved up to the second phalanges of the inner three toes

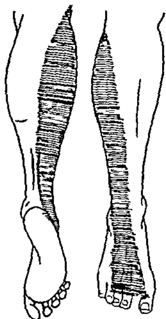


Fig 189 Cutaneous Sensory Distribution of the Common Peroneal (External Popliteal) Nerve

Tibial Nerve

This nerve because of its deeper course is less liable to injury It is also less likely to be involved in neuritis

Signs and Symptoms

1 Patient cannot stand on tiptoes the foot and toes cannot be plantar fixed
2 Toes cannot be abducted or adducted
3 Talipes calcaneus results
4 In walking there is no spring in the patient s step for he cannot lift his heel from the ground
5 Abduction of the foot is weak but is not lost
6 The foot may be edematous and discolored
7 Hyperkeratoses and ulceration are common
8 Dorsal flexion of the proximal phalages results in claw foot
9 Absent ankle jerk
10 Cutaneous sensibility is lost over the sole except at the inner border the lateral surface of the heel the plantar surface of the toes, and, sometimes, over part of the distal phalanges
11 Pain may be very severe and causalgia is not uncommon
12 Contractures from fibrosis may deform the foot

Posterior Tibial Nerve

This is the continuation of the internal popliteal nerve into the calf Involvement produces a paralysis of all the muscles of the sole Causalgia frequently accompanies the lesion and contractures are common In incomplete lesions dissociated paralyses may occur

Small Sciatic Nerve

This is a purely sensory nerve Its division causes loss of cutaneous sensitibility over the back of the thigh, buttock and perineum

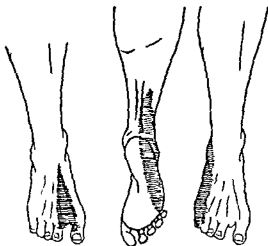


Fig 190 Fig 191

Fig 190 Cutaneous Sensory Distribution of the Deep Peroneal (Anterior Tibial) Nerve

Fig 191 Cutaneous Sensory Distribution of the Saphenous Nerve

Gluteal Nerves

The superior and inferior gluteal nerves are branches of the sacral plexus They may be involved in fractures of the pelvis or sacrum and by tumors in the same areas Standing and walking are not affected but climbing stairs and rising from a sitting or recumbent position are difficult

Genitocrural Nerve

The genitocrural nerve supplies sensory fibers to the scrotum and to an area of skin in the middle of the upper part of the thigh Its division results in no loss of sensation but may cause pain in the upper part of the thigh and scrotum





FIG 192 FIG 193

FIG 192 Cutaneous Sensory Distribution of the Genitocrural Nerve

FIG 193 Cutaneous Sensory Distribution of the Iliohypogastric Nerve

Iliohypogastric and Ilioinguinal Nerves

These nerves arise from the first lumbar root They are sensory but have no exclusive area of sensory supply Therefore injury to them results in no loss of cutaneous sensibility but there may be pains localized to the upper parts of the outer and inner aspects of the thigh

GENERAL CONSIDERATIONS IN PERIPHERAL NERVE INJURIES

History

In the examination of a patient with a peripheral nerve injury a complete history is important for since many of these cases later come to court it is necessary to establish the authenticity of the events surrounding the original injury The following information should be obtained

1 The date hour and location as well as what the patient was doing at the time of injury
2 The site and nature of the injury
3 Was paralysis immediate or did it come on gradually?
4 Enquiry should be made into all subjective and objective symptoms at the time of the occurrence of the injury
5 The progress of the paralysis and the sensory phenomena should be recorded
6 A note should be made of the treatment to date and by whom given as well as of the results
7 The date of any operations should be given with a note of what was done

Examination

A complete physical examination is time well spent for such a procedure has spared much embarrassment in court at a later date In textbooks one group of signs has been attributed to lesions caused by anatomical interruption of the nerve trunk and another to lesions producing gradual or complete interruption of conductivity without anatomical interruption such as would result from compression of tumors or foreign bodies It is generally stated that if the paralysis is immediate injury with a break in continuity of the nerve fibers has occurred If the paralysis appears gradually and there are signs of motor and sensory disturbance with irritation, it is believed that the lesion is due to compression by a tumor callus or scar tissue This differentiation has been considered important and used as a guide to treatment i e, immediate surgical intervention being necessary in the one but could be postponed in the other However the latest texts on war surgery of the nerves insist that such distinctions are artificial inaccurate and misleading and have been abandoned by most observers

The following items should be recorded

1 *The site of entrance and exit* of the wound noting any scar, callus or evidence of neuromas
2 Palpate the nerve trunk itself Is there any induration above or below the level of injury?
3 *Motion* There are many pitfalls in examining for motion since gross movements of the wrist or fingers are possible even with total paralysis of one or more of the nerves, should anastomotic or atypical nerves make up the defect

One should note voluntary motion and not be misled by elastic recoil which may simulate active motion

All deformities such as foot drop, wrist drop claw hand should be studied as well as, certain conditions which may affect the motion about joints such as swellings dislocations, fractures, adhesions, ankylosis, contractures, spasms, loss of tendon or muscle, ischemic paralysis, and the bizarre loss of motion seen in hysteria (See Figure 169)

Lesion of Nerve	Movements Difficult to Simulate
Radial Nerve	Extension of the wrist proximal phalanges of the fingers and thumb
Ulnar Nerve	Abduction of the little finger in a plane with the *palm without flexion of the finger* Extension of the distal phalanges of the fingers with the proximal phalanges in extension
Median Nerve	Flexion of the distal phalanx of the thumb and index finger
Sciatic Nerve (Peroneal portion)	Dorsiflexion of the foot and ankle
	Loss of Reflexes
Musculocutaneous	Biceps jerk is lost
Radial Nerve	Triceps jerk is lost
Sciatic Nerve	Achilles tendon jerk is lost

4 *Objective Sensory Disturbances* The temperature, touch and pressure senses, as well as, vibratior and joint senses should be carefully investigated Charts using the anatomical diagrams (see page 868) should be kept so that comparison can be made at subsequent intervals

5 *Atrophy and Tone* The affected muscles should be compared with the corresponding muscles on the opposite side One should note the presence of any myotactic irritability as manifested by an increase in activity to tapping or other mechanical stimuli This phenomenon is present when muscle fibers are freed from their neural connections

6 A note should be made of any *causalgia* This may begin several weeks after the injury and is manifested by a stabbing piercing, throbbing and burning pain The finger tips may be swollen, the skin is shiny and there may be blisters, papules or changes in the nails

7 *Trophic Changes* Trophic changes may occur after peripheral nerve injuries They may manifest themselves by cyanosis, edema, local ischemia, and gangrene Trophic ulcers may appear Sweat may drip from the finger tips under emotional strain Secondary changes cannot be adequately treated with physiotherapy until after the pain, if it is severe has subsided, and by that time the contractures may be well advanced and resist corrective measures to reestablish movement When it is feared that the secondary changes may produce a greater disability than total loss of nerve function, *alcohol injection of the nerve trunk, or* even actual section of the nerve trunk with immediate suture is recommended

8 *Electrical Examination* This is discussed on page 880

Evidences of Recovery of Function

Sensory Recovery Rapidly recovering lesions do not show dissociation of sensation Touch and pin prick return together Painful sensations on pinching are an early manifestation of recovery The pattern of recovery to pain is characteristic, in that it never returns first within the area of isolated sensory supply of a given nerve, but in the region bordering the adjacent uninjured area the analgesia gradually shrinking toward the center The characteristic features are, a return of pain touch or temperature sense in the isolated sensory supply of the affected nerve of pain, touch, or temperature sense in patches some distance from the area supplied by an adjacent uninjured nerve of pain touch or temperature sense in deep indentations of these modalities in the isolated supply of the nerve or in the border between the sensory supply of two nerves injured simultaneously, and the interlacement of the border of sensory loss of one type of sensation with that of another

Electrical Indications of Recovery The best electrical indications of recovery are an increase of rapidity in response to the galvanic current *Partial lesions showing recovery* before eight months may show a response to

the faradic current before motion returns Sometimes, motion may be possible yet the faradic response is absent

Recovery of Motion Generally in severe lesions some tone returns before there is any voluntary motion The earliest movements are quite clumsy The order of return of function in an injured nerve in severe lesions is (1) return of sensation to pinching or of other sensations over the isolated supply of the nerve (2) spontaneous aching of the muscles (3) return of motion and (4) return of electrical excitability

Treatment of Peripheral Nerve Lesions

The treatment of peripheral nerve injuries is either medical or surgical or both, depending upon the type of injury There is no exact way of determining whether the interruption of the nerve is anatomical or physiological if there is complete loss of function An incomplete lesion may be revealed when subsequent examination shows some return of function following motor sensory or electrical stimulation *If a nerve is completely divided, or is severely compressed or caught in scar tissue the treatment is surgical* This is also the treatment if nerve conduction has been blocked by a neuroma Most authorities have held that from two to three months should be allowed to pass before operating in order that the wound should be free of infection which might militate against successful surgery But since the advent of the sulfonamide drugs early wound healing is more common and exploration and repair are attempted much earlier than was considered feasible Detailed instructions on the surgical treatment of peripheral nerve injuries is beyond the scope of this book and the reader is referred to special texts *Splinting exercise massage* and various forms of *physiotherapy* should as a rule be employed Such measures tend to prevent deformity atrophy and fibrosis and increase nutrition and conserve the functional capacity of the affected muscle until nerve regeneration has taken place

Treatment of Causalgia Causalgia due to simple compression is relieved by freeing the nerve from the surrounding scar tissue and either transplanting the nerve and when possible making a new bed free of scar tissue *Alcohol injection* of nerve trunks in cases of neuritis has been in use since the original work of Schlosser and has earned an important place in the relief of irritative nerve lesions Two or three c c of 60 per cent alcohol are injected into the nerve trunk through a fine needle entered 3 to 4 cm above the lesion In addition the nerve should be freed from all surrounding scar tissue Favorable results have followed periarterial sympathectomy in some cases but more lasting relief from pain can be obtained by a *lumbar sympathectomy* if the leg is involved and if the arm *cervical sympathectomy*

BRAIN TUMORS

Brain tumors are either *neoplastic* or *inflammatory* in origin they press upon contiguous brain tissue and increasing in size, raise the intracranial pressure there is interference with the circulation of both the blood and cerebrospinal fluid and both general and focal symptoms result

Etiology

The cause of tumors is unknown They may occur at any time from infancy to old age but are most common in middle life and are most common in males

Symptoms of Intracranial Tumors

Most intracranial tumors give rise to *increased intracranial pressure* which manifests itself in certain common symptoms, the most important being *headache vomiting bradycardia* and *papilledema* To these can be added *psychic* or *mental changes convulsions* and *vertigo* The well known triad of *headache vomiting* and *papilledema* should always raise suspicion At first there may be a clouding of consciousness which is accompanied by headache, mental dullness restlessness confusion and insomnia and there may be delirium When the *compression is pronounced* the pulse slows the blood pressure increases and there may be irregular or periodic breathing examination may reveal a choked disk Stupor and coma follow and as coma deepens paralysis of the bulbar center with respiratory paralysis rapid pulse and low blood pressure supervene

Headache Headache may be the first sign of a brain tumor it is the most common symp-

tom of an intracranial tumor (66⅔ per cent) and usually appears at some time or other. It is probably due to stretching of the dura, which is a very sensitive membrane and may be intractable and severe, persistent or paroxysmal, neuralgic, migranous or throbbing. It commonly occurs either upon awakening in the morning when it is worse, or during the night. It may be diffuse or localized. When localized, its position does not always correspond to the location of the tumor though it may be occipital in posterior fossa tumors. It is intensified by excitement, sneezing, coughing or stooping. These factors are known to aggravate intracranial tension. Tenderness to percussion may be very acute over superficial and dural tumors. Lastly, it should be mentioned that *headache may be absent throughout the entire course of a brain tumor*.

Vomiting. Vomiting, a common symptom, appears to be due to the obstruction to the outflow of the cerebrospinal fluid with medullary compression. It is generally present in tumors of the posterior fossa. It occurs usually in the early morning and during the night. It has no connection with eating and is not preceded by nausea, on this account it is often spoken of as being projectile in character.

Vertigo. This may be a true vertigo, or it may be a feeling of confusion or uncertainty. It is present in from 30 to 50 per cent of cases. Vertigo is especially severe with tumors of the cerebellum or cerebellar peduncles, and in such cases may be accompanied by a reeling or staggering gait. Dizziness is common in infratentorial tumors as well as in tumors of the pons, medulla, acoustic nerve or of the cerebello pontine angle. Vomiting and dizziness are frequently seen together, the cause of the vomiting being the anemia of the vasomotor centers as a result of the increased intracranial pressure. Vertigo and tinnitus may be seen as a result of encroachment upon the auditory nerve. The tinnitus may be associated with increasing deafness and is more or less constant. When tinnitus and vertigo are associated with deafness or involvement of the 5th and 7th nerves on the same side, it localizes the tumor in the lateral recess of the cerebellar fossa.

Papilledema. Papilledema is one of the commonest and most characteristic signs of brain tumor. It occurs in about 80 per cent of cases and should be sought in every case of suspected brain tumor. It may be absent but when other signs point to a brain tumor, no importance should be attached to its absence. While generally affecting both eyes, it may be unilateral or unequal in degree on the two sides. Papilledema gives rise to scotomata especially for colors, or to blindness, therefore, it should be considered a medical emergency.

It occurs most commonly in tumors of the pineal gland and quadrigeminal plate, 3rd and 4th ventricles, and posterior fossa, as well as in tumors of the occipital, temporal, parietal and frontal regions. Greater edema tends to be on the side of the tumor, especially in frontal and cerebellar growths. When primary optic atrophy is present without antecedent choked disk, and is accompanied by other manifestations of intracranial pressure, a *supra sellar tumor* should be suspected.

Psychic and Mental Changes. These may or may not occur with intracranial tumors. They are most frequent when the frontal lobes are involved. Drowsiness, yawning, clouding of consciousness and stupor are common. A change in personality with a tendency to coarseness or even immorality, facetiousness and puerility are suggestive of a tumor of the frontal lobe or possibly of the thalamus. Tumors in the region of the third ventricle and the pineal gland often cause hypersomnia. There is often loss of sphincter control in the late stages.

Convulsions. Convulsions are common and most common perhaps in slow growing tumors and in astrocytomas. They are frequently observed in lesions in or near the motor cortex and the temporosphenoidal lobe. Generalized convulsions of epileptiform type may, however, be produced by tumors in almost any part of the brain. Focal epilepsy with muscular twitchings of the side of the face, hand, arm or leg spreading to other members of the same side of the body and giving rise to unconsciousness is suggestive of an intracranial tumor. When a generalized epilepsy begins in late adult life one should consider the possibility of intracranial tumor. Petit mal attacks and psychic equivalents may also be encountered.

Bradycardia. The pulse becomes progressively slower with increasing intracranial pres

sure It is more common in posterior fossa tumors and is probably due to irritation of the vagal centers in the medulla It is of greatest value in diagnosis when the normal heart rate for the patient is known

Others *Cheyne Stokes breathing* may develop in the late stages of brain tumor *Yawning* or *hiccup* may be seen in tumors of the posterior fossa and *fever* in tumors of the hypothalamic area *Glycosuria* may result from tumors of the fourth ventricle and *diabetes insipidus* in lesions in the floor of the third ventricle *Urinary incontinence* may be due to lesions of the basal ganglia or sub thalamic regions

Types of Brain Tumors

The frequency of tumors in a study of Harvey Cushing s statistics of 2023 cases reveals the following figures

	Per cent
Gliomas	42 6
Pituitary adenomas	17 8
Meningiomas	13 4
Neurinoma	8 7
Congenital tumors	5 6
Metastatic and invasive tumors	4 2
Granulomatous tumors	2 2
Blood vessel tumors	2 0
Sarcomas (primary)	0 7
Papillomas (choroid plexus)	0 6
Miscellaneous and unclassified	2 2

Gliomas are the commonest type of tumor of the brain They are rarely discrete and are malignant in behavior Some being highly vascular are the seat of hemorrhages others may undergo cystic degeneration They metastasize to other parts of the brain and spinal cord They nearly always arise within the brain substance and do not affect the meninges

Pituitary Adenomas These should present no diagnostic difficulty as the triad of optic atrophy bitemporal hemianopsia and a greatly enlarged sella turcica are usually present and accompanied by signs of pituitary dysfunction i e amenorrhea in the female loss of libido and feminine distribution of body hair in the male increased carbohydrate tolerance and a lowered basal metabolic rate

Meningiomas These are the most common connective tissue tumors of the brain They are firm encap ulated slow growing and vascular growths whose cells are arranged in whorls They occur along the meningeal vessels and superior longitudinal sinus When they are situated under the frontal lobe mental changes loss of olfactory sense optic nerve atrophy on one side and choking of the disk on the opposite side are present Meningiomas arising from the greater wing of the sphenoid may cause hypertrophy of the bone which pushes the eye forward (unilateral exophthalmos)

Neurinomas Neurinomas or acoustic neuromas which are common cerebellopontine angle growths usually manifest themselves by unilateral tinnitus followed by deafness then numbness of the same side of the face vertigo headache dysarthria failing vision and dysphasia

Objective Findings These are ataxia slow nystagmus and the absence of caloric responses from the affected ear

Cerebral Localization

It is a vital necessity in tumors and inflammatory lesions of the brain to localize the lesion as accurately and as early as possible for upon such depends the success of operative treatment Also unless an early diagnosis is made a slight localizing sign seen in the early stages may di appear when the intracranial pressure rises further Thus it can be said that those *focal signs which appear earliest are of the greatest value for they will more likely be due to the original lesion* It must be remembered that localization of function cannot be calculated in a rigid physiological sense as the signs often overlap and tumors of one area will call forth the localizing signs of another It must be stressed that some tumors give rise to no signs and localization is impossible

Frontal Lobe Tumors These tumors may remain silent for a long period especially if they are situated on the right side The prefrontal region is the seat of the higher psychic functions and intellectual activity Through its connections with the pre Rolandic area it is concerned with the origin of muscular movement The *symptoms* resulting from a tumor in this area are

1 Disturbances of thought, memory reasoning—leading to dementia
2 Facetiousness and jocularity
3 Akinesia or disinclination to move

tom of an intracranial tumor (66⅔ per cent) and usually appears at some time or other It is probably due to stretching of the dura, which is a very sensitive membrane and may be intractable and severe, persistent or paroxysmal, neuralgic, migranous, or throbbing It commonly occurs either upon awakening in the morning when it is worse, or during the night It may be diffuse or localized When localized, its position does not always correspond to the location of the tumor though it may be occipital in posterior fossa tumors It is intensified by excitement, sneezing, coughing, or stooping These factors are known to aggravate intracranial tension Tenderness to percussion may be very acute over superficial and dural tumors Lastly, it should be mentioned that *headache may be absent throughout the entire course of a brain tumor*

Vomiting Vomiting, a common symptom appears to be due to the obstruction to the outflow of the cerebrospinal fluid with medullary compression It is generally present in tumors of the posterior fossa It occurs usually in the early morning and during the night It has no connection with eating and is not preceded by nausea, on this account it is often spoken of as being projectile in character

Vertigo This may be a true vertigo or it may be a feeling of confusion or uncertainty It is present in from 30 to 50 per cent of cases Vertigo is especially severe with tumors of the cerebellum or cerebellar peduncles, and in such cases may be accompanied by a reeling or staggering gait Dizziness is common in infratentorial tumors as well as in tumors of the pons medulla, acoustic nerve or of the cerebello pontine angle Vomiting and dizziness are frequently seen together the cause of the vomiting being the anemia of the vasomotor centers as a result of the increased intracranial pressure Vertigo and tinnitus may be seen as a result of encroachment upon the auditory nerve The tinnitus may be associated with increasing deafness and is more or less constant When tinnitus and vertigo are associated with deafness or involvement of the 5th and 7th nerves on the same side it localizes the tumor in the lateral recess of the cerebellar fossa

Papilledema Papilledema is one of the commonest and most characteristic signs of brain tumor It occurs in about 80 per cent of cases and should be sought in every case of suspected brain tumor It may be absent but when other signs point to a brain tumor no importance should be attached to its absence While generally affecting both eyes it may be unilateral or unequal in degree on the two sides Papilledema gives rise to scotomata especially for colors or to blindness, therefore it should be considered a medical emergency

It occurs most commonly in tumors of the pineal gland and quadrigeminal plate, 3rd and 4th ventricles, and posterior fossa, as well as in tumors of the occipital, temporal parietal and frontal regions Greater edema tends to be on the side of the tumor, especially in frontal and cerebellar growths When primary optic atrophy is present without antecedent choked disk and is accompanied by other manifestations of intracranial pressure, a *supra sellar tumor* should be suspected

Psychic and Mental Changes These may or may not occur with intracranial tumors They are most frequent when the frontal lobes are involved Drowsiness, yawning clouding of consciousness and stupor are common A *change in personality with a tendency* to coarseness or even immorality facetiousness and puerility are suggestive of a tumor of the frontal lobe or possibly of the thalamus Tumors in the region of the third ventricle and the pineal gland often cause hypersomnia There is often loss of sphincter control in the late stages

Convulsions Convulsions are common and most common perhaps in slow growing tumors and in astrocytomas They are frequently observed in lesions in or near the motor cortex and the temporosphenoidal lobe Generalized convulsions of epileptiform type may however be produced by tumors in almost any part of the brain Focal epilepsy with muscular twitchings of the side of the face hand arm or leg spreading to other members of the same side of the body and giving rise to unconsciousness is suggestive *of an intracranial tumor* When a generalized epilepsy begins in late adult life one should consider the possibility of intracranial tumor Petit mal attacks and psychic equivalents may also be encountered

Bradycardia The pulse becomes progressively slower with increasing intracranial pres

2 Understand written questions What time is it? Touch your nose!
3 Does patient speak spontaneously? Errors in speech? Leave out words? Mispronounce? Is he aware of errors in speech? Does he speak in whole sentences or disconnected words? Does he speak in jargon?
4 Does he recognize Coin keys, pen How would you use these articles?
5 Write Write your name and address? Write where you are now! What building city and country!
6 Write to dictation 'Franklin D Roosevelt is the president of the United States
7 Repeat these words April—December—Nineteen hundred forty two Remember Pearl Harbor What significance has the last phrase?
French test phrase Chasseur, sachez chasser Polytechnicien de polytechnique
8 (Patient handed a watch) What time is this watch? Set the hands to read half past twelve!
9 Pick out of this group The pencil The penpoint The rubber band The penny Six cents from the change on the table Match these colors
10 Draw A triangle A right triangle A pentagon
11 Notre Dame Cathedral in Paris is what style of architecture? What is a lintel? What is a stylobate? Who designed the Statue of Liberty? Who are McKim Meade and White?

Tumors of the Motor Cortex 1 If on the face there may be clonic twitchings of the face finger, hands or on or both limbs on the side opposite the lesion As they progress more of the side becomes involved and later unconsciousness and generalized convulsions may supervene

2 Motor weakness monoplegia or hemiplegia may follow

3 A tumor between the frontal lobes and extending backward to involve both para central lobules may involve both leg areas and result in paraplegia

Tumors of the Parietal Lobe The cortex of the parietal lobes receives all types of sensory impulses which are integrated into conscious experience We therefore may find

1 Impaired joint sensation and point discrimination
2 Astereognosis—the patient is unable to recognize the form and the shape of familiar objects This is only pathognomonic of parietal lobe lesions when the paths of sensation in other parts of the brain and the cord are intact
3 Apraxia may occur
4 Loss of finer distinctions between grades of temperature
5 Homonymous hemianopsia if lesion extends medially or laterally and encroaches upon the visual pathway
6 Extension forward into the pre Rolandic area will give rise to hemiparesis and focal convulsions
7 Left sided lesions of supra marginal and angular gyri result in total aphasia with apraxia and alexia
8 Acute destructive lesions of the post-central convolution produce a marked sensory loss in the contralateral half of the body If the destruction is complete, all forms of sensation may be lost Two point discrimination and position sense may be badly impaired permanently The patient may drop objects which he tries to pick up He may burn himself before feeling the sensation of heat

Tumors of the Temporo-Sphenoidal Lobe Right sided cortical tumors are often difficult to localize because their symptoms are produced chiefly by the invasion or implication of the adjacent structures and only to a small degree by true focal lesions The cortex of the temporal lobe is the final center for auditory impulses the cortical area of one side receiving impulses from both sides of the body Thus temporal lobe lesions though they do not cause deafness may cause auditory aphasia At first objects are given the wrong names later jargon speech develops and impairment in reading and writing In addition there may be dreamy drowsy states and general convulsions Visual and auditory hallucinations may appear in the opposite half of the visual field There may be hemianopsia and contralateral quadrantic visual field defects as well as macropsia or micropsia and levitation Deep

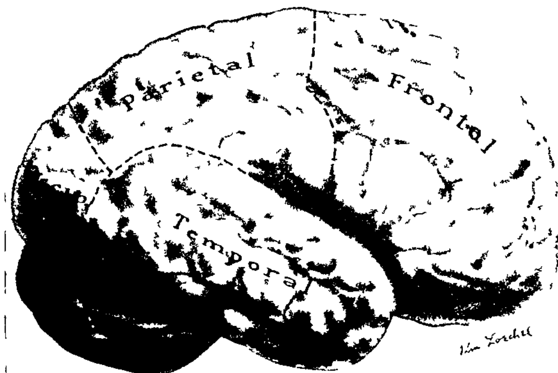


FIG 194 Lobes of the Cerebral Cortex

4 Apraxia or inability to perform a particular movement though the patient is aware of what he wishes to do and has no actual paralysis which prevents his doing it
5 Grasping and groping (premotor area) is elicited by stimulating the palm
6 Incontinence of urine
7 Morbid hunger
8 With downward pressure Loss of smell ocular palsy, exophthalmos impaired sensation in ophthalmic division of the trigeminal nerve on the side of the lesion
9 Ataxia on the side opposite the lesion
10 Paresis on lower half of the face
11 Absent, sluggish or easily exhausted abdominal reflexes on the side opposite to the lesion
12 Aphasia if the tumor is on the left side and extends back to the motor area (On the right side in left handed patients)
13 Anosmia on the side of the lesion
14 Paralysis or convulsions if the tumor presses on the motor cortex

Tumors of the Motor Speech Center Tumors in the motor speech area, which is situated low on the left side in right handed persons and in a corresponding position on the right side in tho e who are left handed cause motor aphasia and if near the motor eye region may cause conjugate deviation of the eyes Aphasia is a difficult subject In testing for motor speech defects one must clearly distinguish aphasia from dysarthria The latter is due to a lack of control of muscles of speech, whereas true aphasia is an inability to understand speech form concepts or to express them It is well to establish whether the patient about to be examined is right or left handed

The following is an example of an examination given a French architect who was picked up by the author at an airport of entry into the United States It was believed that he had motor aphasia and as such would be denied entrance to the country The patient could not speak English and it was necessary to use an interpreter The examination took the following form

1 Understand the spoken word What is your name? Father s name? Give me your hand! Open your mouth! Shut your eye! Your left eye! Touch the tip of your left ear!

2 Hypersomnia (involvement of the central gray matter)
3 Central pain (involvement of the thalamus)
4 Rigidity and hypokinesis (involvement of the extrapyramidal area)
5 Decerebrate signs with Magnus and de Kleijn reflexes
6 Paralysis of vertical gaze
7 Hemiballismus
8 Hypopituitary syndrome with infantilism and hypertrichosis
9 Uncinate olfactory and gustatory syndrome

Tumors of the 4th Ventricle In tumors of the fourth ventricle signs of significance are
1 Choked disk
2 Rigidity of the neck
3 Fixed position of the head
4 Sudden vertigo on a change of position of the head
5 Projectile vomiting

When the vital centers located in the floor of the 4th ventricle are involved sudden death is not very uncommon

Tumors of the Cerebellum Since the pons and medulla and such cranial nerves as take origin in this neighborhood lie in such intimate relation to the cerebellum it is not surprising that cerebellar lesions are frequently accompanied by signs of involvement of these structures The fundamental function of the cerebellum is the coordination of both equilibratory and non equilibratory muscular activity Since this function permits complex movements to be carried out smoothly and synchronously it is easily understood how tumors of the cerebellum may give rise to such symptoms as dizziness and ataxia

The ataxia is more marked on the side of the lesion The patient has a tendency to fall to the affected side If the lesion is in the midline (vermis), there is a tendency for the patient to fall backward or forward *Ataxia in the arms* may be tested by having the patient rapidly pronate and supinate the forearms rapidly On the affected side this cannot be satisfactorily accomplished (*dysdiadochokinesia*) *Dysmetria* and *nystagmus* may also be present The nystagmus is usually lateral but it may be rotary The patient may show the Gordon Holmes rebound phenomenon Altered postures are seen in these patients The head is frequently inclined toward the affected side and held in a fixed position while standing The head may be retracted with the face turned upwards toward the lesion There may be a forward tilt of the shoulder In addition, choked disk, usually coming on early headache and vomiting with nuchal rigidity may be present Pressure on the pons causes signs of pyramidal tract involvement on the opposite with oculomotor paresis on the same side The 6th nerve frequently suffers and internal strabismus paralysis of the facial nerve and deafness is seen on the side of the lesion

Tumors of the Cerebello-Pontine Angle Tumors may arise from the V–VII and VIII cranial nerves The acoustic nerve tumors

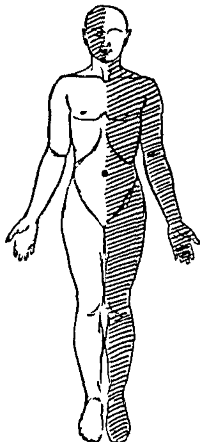


FIG 195 Pontine crossed paralysis A lesion of the pons involving the nucleus of the 7th nerve causing ipsolateral facial paralysis and contralateral hemiplegia

mesial lesions involving the tip of the temporal lobe may cause uncinate attacks with perversions of smell and taste and a champing movement of the jaws or a smacking or spitting movement of the lips Pressure downward on the tentorium may cause homolateral cerebellar symptoms, if the pressure is downward and inward, trigeminal neuralgia may result, and when the oculomotor nerve is affected, there may be fixed, or dilated pupils and ocular palsy on the side of the lesion

Tumors of the Occipital Lobe In these lobes are situated the centers for the final reception and interpretation of visual impressions Each occipital lobe receives visual impulses from the corresponding half of the retina of each eye Lesions usually result in hemianopsia of the homonymous or the quadrantic type The impairment or destruction of the entire calcarine area of one side produces blindness in the opposite visual field (homonymous hemianopsia) If only a part of one calcarine area is destroyed a homonymous field defect corresponding to the involved visual fibers results Irritative lesions of the calcarine area produce visual hallucinations such as flashes *of light or color, or a visual aura and convulsions* not unlike those seen in epilepsy

A tumor of the calcarine fissure is characterized by a contralateral homonymous hemianopsia The field defects at first are partial or quadrantic If the tumor is situated between the occipital lobes and affects both calcarine areas, the hemianopsia may be bilateral (See Fig 172)

Word blindness and the inability to read may result if the angular gyrus is involved

Tumors of the Subcortical Centers and Basal Ganglia Tumors of this area may give only general symptoms for a long time Suggestive *focal symptoms are unilateral tremor* or rigidity, and intractable unilateral pain with signs of increased intracranial pressure Large basal ganglia tumors may give bilateral symptoms

Tumors of the Corpus Striatum Tumors of the corpus striatum may give rise to the following symptoms and disorders

1 Urinary incontinence
2 Excessive sensibility to painful stimuli
3 Spontaneous pains
4 Misinterpretation of light touch or tickling
5 Temperature disturbances
6 Hemiplegia
7 Slowing of voluntary movements The *smaller muscles of the hand particularly*, are affected The patient is clumsy and unable to perform fine movements Weakness of lips palate and tongue result in a slurring speech Monotony of the voice is due to immobility of the larynx The gait is slow and shuffling The patient does not swing his arms as he walks When he sits, he remains still making no spontaneous movement such as crossing the legs
8 Tremor and involuntary movements It must be noted that tremors also occur in cerebellar disease and in hyperthyroidism but in striatal disease the rhythmic tremors are more pronounced The tremor occurs at rest and is exaggerated by any voluntary movement It may be fine or coarse, and as a rule, is slow It usually appears first in the flexors and extensors of the fingers and next in the supinators and pronators of the arm It disappears during sleep and is increased during emo*tional excitement*
9 Change in emotional expression (Mask like facies)

Tumor of the Corpus Callosum In tumors of the corpus callosum one may see mental symptoms not unlike those seen in cerebral arterio sclerosis and general paresis Lesions of the anterior portion are said to produce dementia and apraxia, while involvement of the posterior portion gives rise to delirium delusions hallucinations and agnosia

Encephalographic films are of great diagnostic value i e the anteroposterior view will show the separation of the lateral ventricles

***Tumors of the Midbrain* (Cerebral Peduncles and Colliculi)** Tumors of the anterior part of the peduncles result in *Weber's Syndrome* through impairment of the pyramidal tract and the third cranial nerve Weber s Syndrome is characterized by *a fixed dilated* pupil ptosis external strabismus on the side of the lesion and hemiplegia on the other side

Tumors of the 3rd Ventricle Tumors of the third ventricle give rise to the following symptoms

1 Polyuria adiposity (involvement of the infundibulum)

Tuberculous meningitis may simulate brain tumor but the spinal fluid study will generally aid in making the diagnosis

A *subdural hematoma* may resemble tumor but the bilateral trephine holes used in carrying out ventriculography will almost inevitably disclose a unilateral or a bilateral hematoma and thus confirm the diagnosis before the air study has been done

Retrobulbar neuritis may cause choking of the disk and impaired vision but the spinal fluid pressure is normal and the central scotoma is usually greater than that seen in the usual form of choked disk

Spinal Fluid in Brain Tumors In brain tumors the spinal fluid usually shows an increase of protein, about 100 mg, and increased pressure It must be stressed that in brain tumor spinal punctures are not entirely without danger it having caused deaths in nearly all neurological clinics where it is a routine procedure Merritt states that (1) increase of protein in the spinal fluid and none in the ventricles suggests a tumor in the posterior fossa (2) A high protein content in the spinal fluid and both ventricles suggests a tumor in the third ventricle or corpus callosum (3) If there is increased protein in the spinal fluid and in one ventricle the tumor is on the side which shows increased protein in the ventricular fluid See table LII

Other Diagnostic Criteria of Brain Tumors Horrax (12) has pointed out that there may be be patients who do not demonstrate the well known text book symptoms and signs of brain tumor but who may present a variety of neurological ophthalmological and otological findings such as focal or generalized convulsions visual failure slow in progression and associated with optic atrophy personality change in the absence of cerebral arteriosclerosis or psychosis increased unilateral deafness staggering or a slowly progressive hemiparesis

Diagnostic Study of Suspected Brain Tumor When a brain tumor is suspected the diagnostic study should include

1 A chronologic history
2 Neurologic examination (See page 840)
3 Stereoscopic roentgen studies of the skull
4 Examination of the visual fields and eye grounds
5 Caloric test
6 Electroencephalogram
7 Pneumo-encephalogram
8 Ventriculogram
9 Lumbar puncture with study of spinal fluid, estimation of dynamics and Queckenstedt test
10 Kidney function test if the patient is over 40 years of age
11 Complete blood counts
12 Blood urea and blood sugar determinations
13 Blood Wassermann test (A positive reaction does not signify the presence of a *gumma*)
14 Roentgenologic study of the chest in adults to rule out the possibility of a primary bronchogenic carcinoma
15 Where a pituitary tumor is suspected in addition to the above studies the following may of diagnostic aid
   a Basal metabolic rate
   b Roentgen study of frontal sinuses (bone flap may encroach upon a large sinus)
   c Glucose tolerance test
   d Measure intake and output of fluid in 24 hours
16 Likewise where a cerebellopontine angle tumor is suspected the following may be of diagnostic aid
   a Audiometric test
   b Laryngeal examination
   c Barany test

Treatment of Brain Tumor

As soon as the diagnosis of brain tumor has been made there should be no temporizing with a medical regimen *The treatment is surgical removal* the earlier this is done the better chance the patient has for recovery *Roentgen therapy* deserves a trial in cases of early pituitary adenoma since some are radio-sensitive but the treatment should not be persisted in until optic atrophy has set in In general it may be said that somewhat over half of all brain tumors are suitable for extirpation and of those surviving the operation about 75 per cent should be able to return to a useful life Operative mortality used to range from 15 to 30 per cent Cushing s records are as low as 6½ per cent

comprise 9 per cent of all tumors They take origin from the sheath of the nerve at the internal auditory meatus and cause deafness and tinnitus The tinnitus may assume the nature of roaring, hissing or singing and usually precedes the deafness The VI nerve is next most frequently affected, external rectus paralysis results There may be neuralgia in the region of the trigeminus If the V nerve is damaged some sensory loss will usually occur over the face Involvement of the vestibular nerve is characterized by vertigo and nystagmus, as well as facial weakness and twitching Nystagmus itself, is not pathognomonic of a pontine tumor

The characteristic signs and symptoms according to Barany are a) *absent caloric reactions*, b) spontaneous nystagmus intensified on head movement c) falling in one or other direction, d) inclination of the head to the side of the lesion e) disturbances of equilibrium

Tumors of the Pons Tumors of the pons are characterized by crossed anesthesia of the *face on the side of the lesion and of the body on* the opposite side alternating hemiplegias and paralysis of lateral gaze Strictly unilateral lesions of the pons are uncommon and therefore hemiplegic signs may be present bilaterally and in variable degree Tumors of the pons are always fatal

Tumors of the Medulla *Because of the* vital centers involved these tumors are rapidly fatal Crossed paralyses occurs i e hemiplegia on one side and paralysis of the IX X, XI, or XII cranial nerve on the opposite side There may also be dysarthria atrophy of the tongue, ataxia vertigo, nystagmus and vomiting

Other Types of Intracranial Tumors

Pituitary Adenomata See page 625–632

Pineal Body Tumors These are frequently found in children They give rise to both sexual and intellectual precocity The secondary sex characteristics are developed prematurely *These tumors* cause early increased intracranial pressure and various disturbances of the ocular muscles

Diagnosis of Brain Tumors

With our present knowledge and methods intracranial lesions should offer no great difficulty in respect to their detection and localization If a patient has the well known symptoms and signs of brain tumor including *vomiting, vertigo, headache* and *choked disks*, the burden of proof, according to competent neurologists, is on *one who says the diagnosis* is not brain tumor

Papilledema may occur in *brain abscess hydrocephalus, sinus thrombosis, subarachnoid hemorrhage, meningitis*, and rarely in *encephalitis* The headaches of *migraine, syphilis, hysteria, uremia*, and *sinusitis* should be excluded

Brain abscess may be suspected if there is or has been an infectious process, particularly if it is chronic, such as, *otitis media, chronic mastoiditis, frontal sinusitis* or *bronchiectasis* *When the mode of onset is obscure or the* abscess is from some extracranial source of infection, the diagnosis may not be made until operation Abscesses have as their usual point of localization the frontal or the temporal lobe The finding of many polymorphonuclear cells in the spinal fluid would suggest abscess rather than tumor *Fever is present more often in* abscess the course is more rapid choked disk less likely to be present, and there may be more than one focus

Arachnoiditis (pseudo-tumor) may simulate tumor but with the pressure symptoms and choked disk and other signs of tumor together *with a ventriculogram which reveals* normal sized ventricles in normal position, the differentiation will not be difficult

Cerebral arteriosclerosis and *malignant hypertension* also cause headache and choked disks as well as other pressure symptoms In the case of *malignant hypertension* the blood pressure findings together with the signs of cardiorenal disease will aid in the diagnosis An encephalogram may be indicated when the systolic and diastolic pressures are not unduly elevated *Cerebral softening due to thrombosis* may give rise to mental changes and sensory or motor paralysis It is believed that encephalography and ventriculography offers much here in the differential diagnosis

Neurosyphilis very seldom offers difficulties as the history mental state pupillary signs blood and spinal fluid serologic reaction should point to the diagnosis It should be remembered that a person with syphilis may have a brain tumor as well

sinuses as well as evidence of existing infection Choked disk though it may occur in abscesses is more likely to be present in tumors The subsequent signs and symptoms may simulate a brain tumor There may be an enormous abscess in one cerebellar hemisphere yet cerebellar signs be absent There is usually no fever and, when present is due to activity of the causative focus

If a patient has not a demonstrable septic focus the diagnosis between a tumor and a brain abscess is difficult, to say the least *The spinal fluid findings are not conclusive* In both tumor and abscess the pressure and the protein content are usually increased The spinal fluid of those with tumors occasionally contains a few cells but usually there is none On the contrary, those with brain abscess usually have several or many cells in their spinal fluid When other measures of diagnosis fail ventriculography is of assistance as a means of localization though it is risky and may cause rupture of the abscess

If the history suggests an intracranial lesion as a cause of headache the following measures may be employed to establish the diagnosis

1 Complete physical and neurological examination with the history recorded in the exact chronological order of the appearance and progress of symptoms
2 Blood counts and differential smears
3 Blood cultures to determine the existence of a coexisting septicemia
4 Blood serologic reaction
5 Urinalysis
6 Careful temperature charting
7 Visual field examination and ophthalmoscopic examination of the fundi
8 Stereroscopic roentgen studies of the skull
9 Roentgenogram of the chest for abscess and tumors of the lung
10 Lumbar puncture and examination of cerebrospinal fluid
   a Cell count
   b Globulin
   c Total protein
   d Wassermann reaction
   e Colloidal gold reaction
   f Bacterial cultures
   g Smears of the centrifuged sediment
11 Ventriculography or encephalography

Differential Diagnosis

1 Labyrinthitis
   Vertigo and nystagmus to the healthy side
   Tinnitus aurium
   Loss of hearing
   Loss of response to the caloric test
   Absence of headache and focal signs
2 Sinus Thrombosis
   High remitting fever
   Positive blood culture
   Positive Queckenstedt test may be present
   Remember that an abscess may coexist
3 Epidural abscess Differentiation cannot be made by symptoms The diagnosis is made at operation

Treatment

Before walling off and localization has taken place the *sulfonamides* or penicillin should be given the choice of drug being determined by what organism is present or suspected See chart page 1039 Such treatment may abort an early process and prevent the formation of large lesions When a large walled off abscess is present treatment should be surgical but the drug should be given as well As a rule, operation should be delayed for encapsulation of the abscess if it is within the brain substance, but epidural and subdural abscesses may be drained immediately with impunity No matter how badly the patient looks the abscess should be opened if possible for operation may be the patient s only chance of recovery

EPIDEMIC ENCEPHALITIS (ENCEPHALITIS LETHARGICA)

Encephalitis was first described by Von Economo in 1917 It is an infectious disease of the nervous system, occurring usually in epidemics and affecting usually the mid brain nuclei and extra pyramidal system Its cause is not definitely known but it is believed to be a filterable virus Both sexes of all races and ages are affected The acute epidemic virus encephalitides are similar in their clinical aspects so that differentiation on this basis is not possible except in cases of poliomyelitis Epidemic encephalitis was a fairly definite clinical syndrome when it first appeared but the acute symptoms have changed considerably in the past twenty years

Post-Operative Complications of Brain Tumors

1 *Vomiting* This complication frequently occurs and for this reason the patient should be kept on his side with the head elevated to prevent the aspiration of vomitus The administration of fluids should be stopped and the stomach lavaged through a *small* catheter *Cracked ice* and *ginger ale* are often tolerated when other fluids are promptly vomited The emetic effect of *morphine* should be remembered and the drug used with caution

2 *Post-Operative Bleeding* Staining of the dressings with cerebrospinal fluid or blood should be reported to the physician promptly Intracranial bleeding may manifest itself by stupor drowsiness, a change in the reflexes dilatation of the pupils slow pulse and an elevation of the blood pressure Post operative cerebral edema may be a confusing feature and some advise the use of hypertonic solutions in differentiating between this condition and hemorrhage since in edema, the symptoms may subside following their administration This is not always a safe procedure however and when there is any doubt the wound flap should be elevated

3 *Feeding Difficulties* Mild anorexia and vomiting may supervene and should be combated by exposure to ultra violet light or sun light administration of B complex or the infestion of cod liver oil Feeding through a nasal tube may be necessary

4 *Post-Operative Fever* A recurrence of fever in one whose temperature has been subsiding indicates infection When such occurs its source should be sought a lumbar puncture made and the bladder catheterized Spinal fluid and urine cultures should be made

An operation near the third ventricle and hypothalamus may be followed by a high temperature without demonstrable cause There is little that can be done for it other than the application of ice bags below the chest for hourly periods and reducing the bed covers to a minimum

BRAIN ABSCESS

Brain abscesses are always secondary to a septic focus elsewhere in the body the most common being suppuration in the middle ear mastoid or nasal sinuses Just how the infection extends from the mastoids to the cerebellum or temporal lobe is not clearly understood The next most common secondary foci of brain abscesses is pulmonary disease (lung abscess, bronchiectasis) Other causes are fractures running through the nasal sinuses or mastoid, and any focus followed by septicemia or bacterial endocarditis While infections from contiguous pyogenic foci most often result in abscess within the brain substance it sometime happens that the collection of pus localizes in the region outside the dura, they are then known as epidural abscesses

Otitic abscesses are usually located in the temporal lobe or the cerebellum more often in the former *Epidural abscesses* are generally found over the temporal lobe

Symptoms

These are the general and focal symptoms of an expanding inflammatory lesion The onset is usually gradual with an intermittent low grade fever, loss of weight nausea vomiting bradycardia and focal signs determined by the site of the abscess *Temporal lobe abscesses* if deep may cause homonymous hemianopsia, loss of abdominal and increased deep reflexes with a positive Babinski sign or even signs of hemiplegia Sensory aphasia may be present if the lesion is on the left side speech may be of the jargon type Cerebellar abscesses give rise to occipital headaches pain in the neck ataxia vertigo nystagmus usually evere signs of intracranial pressure and there may be choking of the optic disks (Pressure on the uncinate gyrus may cause anosmia and uncinate fits) Vertigo and vomiting are common Early impairment or loss of corneal reflexes on the side of the lesion and paralysis of the external rectus muscle are secondary signs on the side of the abscess *Frontal lobe abscesses* give rise to general symptoms such as stupor, headache, vomiting and nausea but if the lesion extends backward hemiparesis may follow Terminal symptoms are chills, fever rapid pulse delirium rigidity, stupor convulsions Cheyne Stokes breathing coma and death

Diagnosis

Focal signs are usually present when the abscess is well advanced There is usually a history of infection of the middle ear or nasal

up and outward and the patient be unable to bring them back to their normal position Very young children may show mental deterioration they may be morons or imbeciles while older children may develop severe conduct disorders that may culminate in criminal acts

The Treatment of Encephalitis

The multiplicity of remedies suggested in the literature in itself, shows the lack of agreement regarding treatment in general, it is symptomatic No treatment is of value in the acute stage and only partly efficacious in the sequelae of the disease In the acute stage lumbar puncture should be performed both for diagnosis and as a therapeutic measure if the fluid is under increased pressure and there are signs and symptoms of meningeal irritation To combat and relieve cerebral edema daily intravenous administration of 100 to 200 c c of 25 per cent sucrose is said to be beneficial Attempts at forced spinal fluid drainage by repeated lumbar puncture and by giving large amounts of water by mouth and by intravenous hypotonic solutions is worth trying *Sulfonamides or penicillin are of no value in the treatment* If bulbar symptoms are present oral hygiene is important to prevent aspiration pneumonia

In stuporous patients *tube feeding* will have to be instituted *Dielene* is a good product for this purpose being rich in calories and vitamins *Chloral hydrate* or *paraldehyde* is recommended for delirious or irritable patients The barbiturates are of value for insomnia Neal feels that the administration of *Bulgarian belladonna* root for the chronic stage has been beneficial to many and that the related group of pharmacodynamic drugs merits further intensive study They are particularly useful in treating the rigidity of muscles which is usually more disabling then the tremor One should start with *stramonium* $2\frac{1}{2}$ grains *gradually increasing the dose to 12 to 20 grains* daily *Hyoscine hydrobromide* grain $\frac{1}{150}$ to grain $\frac{1}{75}$ two or three times daily has been of use for the Parkinsonian rigidities with or without tremor *Syntropan* has been used with good results by some especially when a total daily dose of 2 4 Grams was tolerated *Benzedrine sulfate* is valuable in the oculogyric crises and when drowsiness and a lack of energy are important features of the picture

Patients suffering from this disease require individualized care and their treatment must be chiefly symptomatic

OTHER TYPES OF ENCEPHALITIS

Arthropod Borne Virus Types of Encephalitis Equine and St Louis Types

One of the forms of encephalitis which has been prevalent in recent years is *equine encephalomyelitis* Since the equine and St Louis types have much in common they will be discussed together They are caused by two separate viruses which have been found in the mosquito *Culex tarsalis* Both viruses are widely distributed in the western and central United States The infection is acquired apparently only in the seasons of high temperatures In the *St Louis type* the incidence was higher in the older age groups cases being mild or unrecognized among the children and young adults *After an incubation period of five days* there is an acute onset which rapidly progresses into a semicomatose state for a short period followed by a rapid clearing of the sensorium The virus isolated from blood spinal fluid or nervous tissues was shown to be capable of infecting guinea pigs and monkeys It is transmissable by mosquitoes ticks and chicken mites—and by insects particularly *Aedes dorsalis*

In the *equine type* children are the chief sufferers though the disease may be contracted at any age Those over sixty years of age are more susceptible than those in middle life Males are affected predominantly in the age group from 15 to 50 years and this suggests *occupational exposure* *It is more severe than* the St Louis type of encephalitis the residuals are more marked and recovery is slower and is associated with paralysis The virus can be transmitted to the aedes mosquito as well as the pigeon It is believed that barnyards and fowl runs in small towns and rural areas are the principal foci of infection for either the Western equine or the St Louis type of encephalitis Bird migrations have also been questioned as a possible factor Large numbers of domestic animals have been found to possess antibodies for both the Western equine and the St Louis type of encephalitis so it is possible that a wide reservoir exists The

Since 1923 cases have been rare and the diagnosis should be made only after much deliberation and care, since sporadic cases are uncommon A typical syndrome cannot be formulated, because the symptoms are so varied and bizarre During the great epidemic of 1918 to 1923 many cases were wrongly diagnosed as influenza The incubation period is from five to seven days Multiple cases in a family are not common and are rarely traceable to a previous case Second attacks are uncommon It is a winter disease

Observations are pointing to the method of spread of seasonal encephalitis as being through the agency of blood sucking insects Mosquitoes have been incriminated as vectors for the cases in the Yakima valley

Wechsler (13) distinguishes 6 main groups of encephalitis

1 Encephalitis occurring in the course of any disease of the brain
2 Encephalitis occurring in the course of, or a variant of, acute anterior poliomyelitis
3 Encephalitis following or occurring in the course of infectious diseases and in intoxications (arsphenamine encephalitis) This group is also known as acute non purulent or hemorrhagic encephalitis of Strumpell and Leichtenstern
4 Polioencephalitis acuta hemorrhagica superior of Wernicke, or acute alcoholic encephalopathy
5 Acute serous encephalitis
6 Epidemic encephalitis

It is the location of the lesion and the intensity and acuteness of the process which characterize the clinical picture and course Eight groups based upon gross anatomical localization are differentiated (14) They are

1 Lethargic mesencephalic group characterized by stupor, pupillary abnormalities and ocular palsies
2 Hyperkinetic and basal ganglia group with abnormal movements such as tics myoclonias, choreic athetoid and dystonic movements
3 Psychotic group with cerebral symptoms mania delirium, catatonia and stupor
4 Basal ganglia or substantia nigra group with Parkinsonian rigidity and tremor
5 Meningitic group closely simulating tuberculous meningitis
6 Bulbar group, often fatal with paralysis of deglutition, respiratory and cardiac failure
7 Neuritic group
8 Myelitic and myeloradiculitic group (disseminated encephalomyelitis)

Differential Diagnosis of the Various Forms of Encephalitis

See the appended chart for the differential diagnostic chart of the various encephalitides on page 932

The Diagnosis of Encephalitis

In general the diagnosis of encephalitis is based upon the following chief signs and symptoms

1 Acute nervous disease
2 Fever
3 Insomnia or drowsiness
4 Spinal fluid findings (See table on page 933)
5 Pupillary and/or ocular signs
6 Radicular pains
7 Involuntary movements
8 Development of Parkinsonian syndrome with rigidities or loss of associated and automatic movements

Encephalitis lethargica has been used as a scrap basket diagnosis too frequently in the past for insufficiently studied conditions

Course and Prognosis

The course is either acute subacute or chronic The course of acute encephalitis has changed over a period of twenty years In the early epidemics the mortality reached 20 per cent Lately the disease has been found to run a more benign course although the incidence of chronic encephalitis has not been materially lessened The important point in this disease is what happens to the survivor The mortality in the sporadic cases is low compared to that in the epidemic type The *prognosis* should always be guarded since severe cases may recover while mild cases may merge into Parkinson s disease in which there is gradually increasing rigidity of the body associated with tremor of the head and extremities loss of associated movements and increased salivation *Oculogyric crises* may develop in which the eyes may suddenly turn

TABLE LVIII—*Concluded*

Type	Spinal Fluid Manifestation: Color	Cell Type	Number	Pressure	Organisms	Globulin	Sugar	Chlorides	Isolation of Virus from Central Nervous System	Neutralization of Virus with Serum of Patient	Reproduction of Disease in Animals	Muscle Pain	Upper Motor Neurone Signs	Spastic Paralysis	Lower Motor Neurone Reflexes	Flaccid Paralysis	Meningeal	Somnolence Drowsy Comatose	Myoclonic Choreiform Movements Hyperkinetic	Nystagmus	Muscle Paralysis	Optic Nerve Involvement	Other Cranial Nerves	Vertigo	Psychic, Memory and Attention Poor
Benign Lymphocytic Choriomeningitis	Clear to opaque	Lymph	100-3,000	+	−	±	−	Normal or slight decrease	+	+	+	−	−	−	−	−	+	+	−	−	−	−	−	−	−
St. Louis Type	Clear	Lymph	50-1,000	+	−	+	±	No significant change	+	+	+	−	+	+	−	−	+	+	+	−	−	−	−?	+	+
Equine Encephalomyelitis	Clear or ground glass	Leucocyte	200-2,000	±	−	++++	−	N.S.	+	+	+	−	+	−	+	+?	±	+	+	−?	−?	−	7th	−	+
Japanese Type B	Clear	Lymph	100	±	−	+	−	N.S.	+	+	+	−	±	−	−	−	+	+	−	−	−	−	−	−	+
P… Encephalomyelitis	Clear	Lymph but may be leucocyte at first	20-1,000	±	−	+	−	N.S.	+	+	+	+	−	−	+	+	+	±	±	±	±	−	Anyone	−	−
Lethargic Encephalitis	Clear	Lymphocytes	100-?00	±	−	+	−	N.S.	−	−	−	−	+	±	−	±	+	+	+	+	+	±	Others	+	+
Tuberculous Meningitis	Clear to opaque	Lymph but may be leucocytes at first	30-100	±	+	+++	D	Decreased	Organism can be isolated	−	−	±	+	+	+	+	+	+	±	+	+	±	Others	−	−
Syphilitic Meningitis	Clear	Lymph	Normal to 500	±	−	++		N.S.	Positive Wassermann	−	−	−	−	−	−	±	±	±	±	±	+	±	±	−	±
Schilder's Disease	Clear	Normal	Normal	−		−	−	N.S.	−	−	−	+	+	+	−	−	−	−	+	−	−	+?	−	−	+
Australian X Disease	Clear	Lymph	100	±	−	+	−	N.S.	+	+	+	−	+	±	−	−	±	+	+	−	−	−	±	−	+
Acute Disseminated Encephalomyelitis and Acute Multiple Sclerosis	Clear	Negative or lymphocytes	Normal or slight increase	−	−	+	−	N.S.	−	−	−	+	±	−	+	+	±	−	±	−	±	+	Others	−	−

± = may be present though usually not

TABLE LVIII

Differential Diagnosis of the Various Forms of Encephalitis

Type	Age	Sex	Time	Locale	Mortality	Temperature	Pulse	Respiration	Onset	Progress
Benign Lymphocytic Choriomeningitis	Any	Any	Any	Any	0	High moderate	Follows temperature	Follows temperature	Abrupt	Rapid
St Louis Type	Any	Any	Summer	Near St Louis near stream	20%	High	Follows temperature	Follows temperature	Abrupt to 1 5 days	Usually rapid
Equine Encephalomyelitis	Mostly children	Any	Summer	Where epizootic disease in animals	0%	High	Follows temperature	Follows temperature	Abrupt	Rapid
Japanese Type B	Older people	Any	Summer	Japan	60%	High	Follows temperature	Follows temperature	Abrupt	Rapid
Poliencephalomyelitis	Mostly children	Any	Summer	Any	70% bulb	Higher lower	Normal or fast	Normal or slow deep	Abrupt	Usually rapid
Lethargic Encephalitis	3-4th decade	Any	Winter—Spring	Any	25–40%	Moderate—occ high	Follows temperature	Follows temperature	Abrupt	Variable slow or rapid
Tuberculous Meningitis	Usually young	Any	Any	Any with history of exposure	100%	Normal then high	Follows temperature	Irregular or Biot's type	Gradual	Rapid at end
Syphilis Meningitis	Usually older	Any	Any	Any	30%	Normal or slightly increased	Follows temperature	Follows temperature	Abrupt or gradual	Slow
Schilder's Disease	Usually young	More male	Any	Any	100%	Low	Not abnormal	Not abnormal till end	Slow	Variable
Australian X Disease	50 per cent under 5 years of age	More males	Summer	Australia	70%	High	Follows temperature	Follows temperature	Abrupt	Rapid
Acute Disseminated Encephalomyelitis and Acute Multiple Sclerosis	Any	Any	Any	Any	10%	Low or high	Follows temperature	Follows temperature	Abrupt or gradual	Slow or rapid

Table from Toomey, J. A.: J. A. M. A. 115: 1985, 1940.

represent 50 per cent or more of the total cells Later, lymphocytes predominate Adamson and Dubo (16) and Hammon(17) state that the presence of from 5 to 15 per cent of large mononuclear cells on or after the third day is an important differential finding in a fluid otherwise similar to that of poliomyelitis The sugar content is normal and globulin or total protein tests may show a slight increase

Differential Diagnosis Consult the chart on page 932–933

Treatment The treatment for this group of encephalitides is symptomatic *Lumbar puncture* should be performed as often as necessary in order to maintain a normal pressure *Fluids* should be given freely parenterally if necessary In the early acute fulminating stage little can be done Those who survive the period of high temperature must be assisted through an interval when complications are common and inflammation and edema of the brain are slowly subsiding Proper attention to oral hygiene is necessary and urinary retention should be treated Hammon (18) advises the administration of one of the sulfonamides in adequate dosage as a prophylactic against urinary tract infection or pneumonia since they are two common and fatal complications He adds If the patient by factors apparently *beyond our control* survives the acute stage (usually two to four days) by proper care *within our control* he can be helped to survive the next stage

Prophylaxis Specific chick embryo *vaccines* for both the eastern and western types of virus are available for human use It is recommended that 1 c c be given subcutaneously in two doses one week apart The patient should be observed for an hour following vaccination and if any anaphylactic reaction develops adrenalin should be administered

Mosquito control and protection against mosquito bites appear to be a more reasonable prophylaxis than yearly vaccination as protection would then be secured against each of several possible viruses present during an epidemic Vaccination for all types is not available

JAPANESE B ENCEPHALITIS

The virus of this disease resembles in many respects the etiologic agent of St Louis encephalitis The disease has been prevalent in Japan since the beginning of the century and perhaps occurred in the last century The greatest incidence is found in the three prefectures lying on the coast of the Inland Sea There have been small outbreaks in Formosa, the southern Ryukyu Islands eastern China and eastern U S S R Case fatality rates range from 42 to 75 per cent averaging about 69 per cent While the rate is high in all ages, it is higher in the very young and the older age groups There is an increase in morbidity with advance in years It is a summer disease the incidence being greatest in the months of August and September An increase in the number of cases frequently follows a rainy period

Transmission Studies strongly suggest that the disease is mosquito-borne The virus of Japanese B encephalitis has been isolated from *Culex pipiens* var *pallens* and *Culex tritaeniorhynchus* Both the culicine species as well as *Aedes togoi Theobald Aedes albopictus* and *Aedes japonicus Theobald* are capable of transmitting the disease to susceptible mice and monkeys in laboratory experiments Hammon has demonstrated that six species of mosquitoes found in California can transmit the virus of Japanese B encephalitis to animals Thus once introduced into this country the disease could readily spread under the favorable conditions which exist in wide areas The virus of Japanese B encephalitis probably has its reservoirs in mammals and birds

Clinical Course The clinical course of the disease varies considerably among different individuals and in different age groups It is likely to be severe when it occurs in infants and in the aged The onset is sudden and is usually characterized by fever severe headache malaise backache abdominal pains nausea and vomiting In some instances there may be immediate encephalitic manifestations such as severe headache rigidity of the neck and back tremors mental confusion difficulty in phonation and stupor

The temperature may reach 102 F to 106°F with a peak on the second to fourth day of the illness At the height of the fever encephalitic symptoms commonly arise and are often associated with nystagmus slight strabismus transient and variable tendon reflex

Western type has been associated with the *culex tarsalis* season

Fatality rates vary from 5 to 22 per cent depending upon the age group They are highest under two years and over fifty years of age

Signs and Symptoms The form seen in infants differs from that in adults therefore each will be discussed separately

Infants The disease usually commences between ten days and 6 months of age although it has been observed at four days in this instance it was most likely due to an intra uterine infection The onset is sudden and characterized by vomiting, twitchings, rigidity, nuchal rigidity bulging fontanelles, convulsions, and severe dehydration The temperature usually rises to 103° or even 105°F, remains at this level for from 24 to 48 hours and then falls to normal There may be convulsions and twitchings unilateral or bilateral but with the fall in temperature the motor symptoms decrease though they may persist for a short time after the temperature has reached normal Strabismus and cyanosis may appear

In the Eastern type of equine encephalitis the disease is more fulminating and severe death resulting in over 50 per cent of the cases and within 48 hours of the onset

Older Children and Adults Children over four years of age and adults present a clinical picture different from that seen in infants Only in rare instances are there convulsions and twitchings Ordinarily the onset suggests an acute systemic infection It usually begins with a headache malaise chills, fever, backache and some abdominal distress The *temperature* rises to 101° or 102 F in mild cases and to 106°F in severe cases There may be an accompanying nausea and vomiting and signs of an upper respiratory infection The temperature reaches its peak by the second day sometimes the fourth and after a few days it falls by lysis At the peak of the fever signs of encephalitis appear There are severe headache mental lethargy and slow motor responses In some cases stupor may supervene and the patient will have to be roused repeatedly to answer questions There is usually some slight nuchal rigidity as well as rigidity of the back The pupils are small but contract further to light Ankle clonus is sometimes found superficial abdominal reflexes are absent or unilateral Scrotal and plantar reflexes may be absent During the next few days speech difficulties increase and there may be complete aphasia Intention tremors of the hand and mandible are seen Deep stuporous sleep, or even coma may ensue The stuporous patient can be aroused to speak or recognize people, but will immediately lapse into stupor

In the severe form, edema of the face as well as spasticity convulsions and twitchings are common The spasticity and other motor symptoms improve with the general condition Rarely there are deafness, monoplegias, spastic hemiplegias nystagmus diplopia, and amblyopia

Death occurs most frequently either within the first two three or four days from a fulminating type of infection, or later when it is due to complications these are usually the cause of death in the aged Convalescence requires months for complete recovery after the severe cases Some residual manifestations are seen in old patients and consist mostly of tremor insomnia mental deficiency, weakness and psychoses

Diagnosis The final diagnosis depends upon specific biological tests and for this reason and also for the sake of treatment, the patient should be sent to a hospital when at all possible

Neutralization Test Ten c c of blood are drawn using dry sterile equipment and no anticoagulants nor preservative When it is necessary to ship the sample to the laboratory serum alone should be sent otherwise hemolysis may occur Two specimens are required One as soon as the diagnosis is suspected and the other thirty days later An intermediate sample drawn from eight to fifteen days after the onset of the symptoms may aid in arriving at an early diagnosis

Complement Fixation Test This is a fairly recent test (Casals and Palacios (19)) and gives quicker results

Lumbar Puncture The pressure is usually slightly or moderately elevated The total cell count varies from 15 to 1000 but is usually between 25 and 500 During the first three days of the illness polymorphonuclears may

disease can be transmitted by the respiratory route it is advised that the precautions usually observed in diseases of the respiratory tract be maintained

The general principles of mosquito control should be applied meticulously The Russians have produced a vaccine which has proved effective in controlling the disease in eastern U S S R Sabin has developed a vaccine which has been shown capable of protecting experimental animals

Infantile Toxoplasmic Encephalomyelitis

Wolf and his co workers have reported a case of granulomatous encephalomyelitis due to the protozoon *Toxoplasma hominis* It has since been reported by others and de scribed as a generalized parasitic infestation which in adults is predominantly pulmonary (Pinkerton and Henderson (19)) and appears as an acute encephalitis in older children (Sabin) (20) It is believed that many cases begin as a prenatal toxoplasmosis In a recent paper (21) Wolf and co workers conclude that toxoplasmic encephalomyelitis is not a rare disease as previously believed They state that the mode of transmission to man is un known Multiple cerebral calcifications in infants and young children should suggest the diagnosis

Diagnostic Criteria of Infantile Toxoplasmic Encephalomyelitis

1 A history of symptoms as described below at birth or during early infancy
2 Varied neurologic symptoms including hydrocephalus and convulsions
3 Chorioretinitis frequently in the region of the macula yellowish white or reddish brown round or oval slightly depressed or elevated patches with irregular spotty often marginal pigmentation
4 Roentgenographic demonstration of mul tiple cerebral calcification
5 Determination by pneumoencephalog graphy of hydrocephalus which is not apparent clinically
6 Xanthochromia round cell pleocytoses and high protein content of the spinal fluid
7 The recovery of toxoplasmas from the blood or spinal fluid of rabbits or mice or of both after intraperitoneal or intra cerebral inoculation
8 The demonstration of toxoplasma—neu tralizing antibodies in the blood of the infant or of the mother

Post Infectious Encephalitis

This group is most common in children and is sometimes seen as a complication of the exanthemata, vaccination for smallpox, anti rabic inoculation and of various intoxications such as acute alcoholic polioencephalitis of Wernicke and arsphenamine encephalitis

Acute Hemorrhagic Encephalitis This con dition is characterized by the presence of an inflammatory reaction and hemorrhagic foci scattered throughout the mid brain cerebrum pons medulla and aqueduct The disease usually affects children but is seen also in adults

Signs and Symptoms The onset is usually sudden with convulsions and a rapidly rising fever There may be a history of a previous upper respiratory infection or headache mental dullness or irritability may precede the onset by a few days Stupor and uncon sciousness soon follow The pulse is rapid and the respirations usually irregular There may be a moderate amount of nuchal rigidity It is not uncommon for convulsions to usher in the disease The convulsions are long, severe and generalized They may be repeated fre quently and not unusually they are unilateral After they have ceased the fever subsides and complete hemiplegia may appear if the disease goes on to recovery or becomes chronic In stead of hemiplegia there may be monoplegia ocular or other cranial nerve palsy hemi anopsia cerebellar ataxia and nystagmus The disease may progress rapidly and end fatally in from a few days to a week The spinal fluid throughout the course of the disease remains normal Unlike the transient hemiplegias which occasionally follow a con vulsion from any cause the hemiplegia in this condition is recovered from slowly and often imperfectly The resultant mono- and hemi plegias are generally permanent

Prognosis In those cases with high fever and coma the prognosis is grave Epilepsy and mental deterioration are common sequelae developing in about 70 per cent of the cases

changes The pupils may become contracted and respond poorly to light Perspiration is profuse and there may be retention of urine During the following few days, the symptoms and signs may progress to coma and death In the event of an overwhelming infection death may occur within the first two days of the disease It usually occurs from the fifth to the seventh day and as a result of complications such as bronchopneumonia or uremia

In those cases which recover improvement in the neurological symptoms and signs is noted as the temperature approaches normal which is commonly five to fourteen days after onset The sensorium may remain clouded for weeks and convalescence may proceed very slowly Permanent residual changes are frequent in the very young and in elderly individuals

Diagnosis The diagnosis may be established in a laboratory equipped to do virus studies by demonstrating an increase in antibody titer during the course of the illness Where this is not possible the clinician will have to make the diagnosis on the basis of the clinical picture, presence in an area of endemicity, and a careful and complete examination of the spinal fluid Sterile serum should be sent to a reliable laboratory for confirmation of the diagnosis Samples of 10 c c each should be obtained for this purpose during the first week at the end of the second week and if possible at the end of the fourth or fifth week

There is usually a slight to moderate increase in the pressure of the spinal fluid The white cell count of the fluid varies from 25 to 500 per cu mm During the early phase of the illness fifty per cent or more of the cells may be polymorphonuclear leucocytes There is a subsequent gradual relative increase in the number of lymphocytes Total protein and globulin are usually slightly increased The presence of from 5 to 15 per cent of large mononuclear cells after the first two to three days of illness is of diagnostic significance Sugar remains at normal levels

Differential Diagnosis During the early acute stage many diseases may be simulated by Japanese B' encephalitis Following the appearance of definite encephalitic symptoms and signs, the diagnosis can usually be made without great difficulty The following conditions which may be confused with Japanese "B" encephalitis should be excluded *malaria, dengue, typhoid fever, heat stroke, influenza, syphilis early purulent meningitis, tuberculous meningitis, lymphocytic choriomeningitis, poliomyelitis, and post infectious encephalitis*

The absence of plasmodia on repeated thick and thin blood smears will exclude malaria Meningitis may be differentiated by the changes in the spinal fluid Negative serological tests will exclude syphilis, typhoid fever and lymphocytic choriomeningitis The sensorium is usually clear in poliomyelitis The differentiation between post infectious and Japanese "B" encephalitis may be very difficult

Treatment The treatment is symptomatic but should be particularly directed toward the prevention and proper management of complications, the most important of which is bronchopneumonia These cases should be transferred to a hospital where they can have the benefit of constant nursing care and attention Lumbar puncture is done at sufficient intervals to maintain a normal spinal fluid pressure In the event of elevated pressure, hypertonic glucose or concentrated serum albumin may be administered intravenously At least 3 000 to 4 000 c c of fluid should be given daily or sufficient to maintain a urinary output of from 1 500 to 2,000 c c It may be necessary to supplement oral fluids with intravenous fluids The diet can be adapted to the condition of the patient, in the event of prolonged illness liberal amounts of protein should be included if nutrition is to be maintained Sluggish stuporous or comatose patients must be turned in bed regularly to prevent hypostatic congestion of the lungs and pressure sores In addition care should be taken to keep their throats free from mucus Pulmonary or urinary tract complications should be anticipated and treated promptly if they arise In the event of secondary infections, the sulfonamides or penicillin should be used

Prevention Since the disease can be transmitted by the mosquito patients should be screened at least during the febrile stage While it is not known definitely whether the

signs The cerebrospinal fluid shows increased pressure cells and globulin

Less Common Types In recent years a number of encephalitides having much in common regarding their signs and symptoms have been described In most of these a then disappear spontaneously though there may be remissions They are accompanied by emotional distress the patient may turn the head backward forward or to one or other side and there is usually propulsion or retropulsion if he is standing when the attack begins

TABLE LIX

Diagnosis of the Parkinson Syndrome According to Etiology

	Paralysis Agitans	Postenceph litic	Syphilitic
Age	Over 50 and usually over 60	Any age	Any age
History	None of encephalitis	History not always obtained from patient	Positive serology or history of chancre
Mode of Onset	Gradual	Gradual	Gradual
Course	Affects one extremity first then spreads Does not affect head	Same	Same
Other Symptoms		Palsies and oculogyric crises	Clinical manifestations of syphilis
Spinal Fluid	Negative	Sugar increased in relation to blood sugar	Usually strongly positive
	Traumatic	**Vascular Accident**	**Senile or Family Tremor**
Age	Any age	About 50 years	Begins about 50 years
History	Recent trauma to head	Hypertension	Usually family history
Mode of Onset	Rapid	Rapid	Gradual
Course	Same as paralysis agitans	Same	Affects head first, later affecting both hands
Other Symptoms	Post concussion syndrome with headache dizziness	Partial hemiplegia and pseudobulbar palsy	Neurologic examination essentially negative
Spinal Fluid	Negative or it may contain blood	Same	Essentially negative

(Table from Stieglitz Geriatric Medicine W B Saunders Co Philadelphia 1943 p 287)

specific virus can be recovered and isolated from the central nervous system neutralized with specific antisera and the disease reproduced by injection into laboratory animals

Postencephalitic Syndrome

It is said that about 50 per cent of patients with encephalitis lethargica develop postencephalitic Parkinsonism in from one to five years It spares no age and is characterized by marked rigidity followed by tremor The facial features are mask like and drooling is common There is a lack of convergence and oculogyric crises in which the eyes are deviated upward and outward are common There may be pain in the eyes but some relief may be obtained by closing the lids especially when the patient is recumbent These oculogyric crises last from a few months to years and It is usually precipitated by emotional excitement

Diagnosis When this condition is suspected a careful history should be taken There may or may not have been a history of an attack of encephalitis or it may have been erroneously called influenza Particular inquiry should be made about any past illness accompanied by (1) fever (2) delirium (3) sleep disturbances such as lethargy hypersomnia or reversal of the normal sleep rhythm and (4) ocular disturbance such as double vision or strabismus The condition when accompanied by the typical posture shuffling gait tremors mask like facies and rigidity is easily diagnosed One should note the patient as he undresses and walks toward the examiner for the automatic movements of the upper extremities which normally accompany

Treatment No treatment is of any value in the acute stage Orthopedic measures should be directed toward the residual hemiplegia

Acute Alcoholic Polioencephalitis of Wernicke There is definite clinical pathological, and experimental evidence for the statement that vitamin deficiency is at the basis of the degenerative and hemorrhagic process which, in this condition, is limited to the cerebral aqueduct of Sylvius Wortis and co workers have concluded (22) after clinical and chemical studies that this syndrome is constantly associated with a disturbance in pyruvic acid metabolism A deficiency of B complex accounts for some forms of encephalopathy and nicotinic acid deficiency for others

Signs and Symptoms

The onset may be acute or there may be some prodromal symptoms such as headache, vomiting somnolence, and ocular palsies Simple delirium may be present but it is not generally associated with hallucinosis or other acute alcoholic symptoms Ataxia is frequently present The main signs consist of paralysis of the ocular muscles and loss of associated ocular movements Optic neuritis and nystagmus may occasionally occur Mental symptoms from simple psychotic phenomena to the Korsakoff syndrome may appear When the red nucleus and its connections are destroyed tremor and rigidity may be present The course is quite irregular death frequently resulting within a week but there may be recovery with or without sequelae

Treatment

Investigation seems to suggest that abstinence from alcohol is not a factor in the onset of delirium tremens and thus alcohol need not be given to these patients as a part of the therapeutic regimen *Thiamine* and *nicotinic acid* should be given intravenously in large amounts A *high caloric diet maintenance of the electrolyte balance* and *sedatives* constitute the treatment Bloomberg in a report of 56 cases (23) finds *benzedrine sulfate* useful He has used up to 140 mg daily The drug combats general malaise and depression, hospitalization can be avoided, establishment of rapport with the physician is more easily accomplished and changes in mood less pronounced Berkwitz (24) states *faradic shock therapy* promptly removes the acute psychotic symptoms in most cases and lessens the need of undesirable protective measures, such as chemical and physical restraints

Arsphenamine Encephalitis While relatively rare, this is a very serious condition following the administration of arsphenamine The symptoms usually occur within a few hours after administration of the drug and consist of drowsiness, apathy delirium, and coma Convulsions sometimes occur and the breathing may be stertorous Death may follow within 48 hours The pathologic picture is that of 'alcoholic wet brain" with multiple scattered hemorrhages

Treatment The best treatment is *adrenalin* 1 1000, 5 to 10 drops injected intravenously every few hours 100 c c of 10 per cent glucose should be also injected *Sodium thiosulfate* 0 5 gm intravenously is recommended though the results are debatable A new preparation, B A L has shown strikingly curative results and is the preferred treatment when it can be secured

Post-Vaccinal Encephalitis Encephalitis may follow vaccination in from 10 days to 2 weeks It is characterized by a rapid and stormy course terminating fatally, or with recovery which may or may not be followed by sequelae similar to those of epidemic encephalitis The symptoms closely resemble the exanthemata and may be ushered in by convulsions vomiting and headache soon followed by prostration coma and paralysis of the extremities and cerebral nerve palsies Trismus meningismus and retention or incontinence of urine occasionally occurs The mortality is between 30 and 50 per cent The treatment is symptomatic

Lead Encephalopathy This is a dreaded complication of lead poisoning It is a diffuse, organic acute cerebral condition Headache is an early symptom others are convulsions, delirium memory defects psychoses hemiplegia cranial nerve palsies optic neuritis hemianopsia blindness and mild meningitic

signs The cerebrospinal fluid shows increased pressure cells and globulin

Less Common Types. In recent years a number of encephalitides having much in common regarding their signs and symptoms have been described In most of these a specific virus can be recovered and isolated from the central nervous system neutralized with specific antisera and the disease reproduced by injection into laboratory animals

Postencephalitic Syndrome

It is said that about 50 per cent of patients with encephalitis lethargica develop post encephalitic Parkinsonism in from one to five years It spares no age and is characterized by marked rigidity followed by tremor The facial features are mask like and drooling is common There is a lack of convergence and oculogyric crises in which the eyes are deviated upward and outward are common. There may be pain in the eyes but some relief may be obtained by closing the lids especially when the patient is recumbent. These oculogyric crises last from a few months to years and then disappear spontaneously though there may be remissions They are accompanied by emotional distress the patient may turn the head backward forward or to one or other side and there is usually propulsion or retropulsion if he is standing when the attack begins It is usually precipitated by emotional excitement

TABLE LIX

Diagnosis of the Parkinson Syndrome According to Etiology

	Paralysis Agitans	Postencephalitic	Syphilitic
Age	Over 50 and usually over 60	Any age	Any age
History	None of encephalitis	History not always obtained from patient	Positive serology or history of chancre
Mode of Onset	Gradual	Gradual	Gradual
Course	Affects one extremity first then spreads Does not affect head	Same	Same
Other Symptoms		Palsies and oculogyric crises	Clinical manifestations of syphilis
Spinal Fluid	Negative	Sugar increased in relation to blood sugar	Usually strongly positive
	Traumatic	**Vascular Accident**	**Senile or Family Tremor**
Age	Any age	About 50 years	Begins about 50 years
History	Recent trauma to head	Hypertension	Usually family history
Mode of Onset	Rapid	Rapid	Gradual
Course	Same as paralysis agitans	Same	Affects head first later affecting both hands
Other Symptoms	Post-concussion syndrome with headache dizziness	Partial hemiplegia and pseudobulbar palsy	Neurologic examination essentially negative
Spinal Fluid	Negative or it may contain blood	Same	Essentially negative

(Table from Stieglitz Geriatric Medicine W B Saunders Co Philadelphia 1943 p 287)

Diagnosis. When this condition is suspected a careful history should be taken. There may or may not have been a history of an attack of encephalitis or it may have been erroneously called influenza Particular inquiry should be made about any past illness accompanied by (1) fever (2) delirium (3) sleep disturbances such as lethargy hypersomnia or reversal of the normal sleep rhythm and (4) ocular disturbance such as double vision or strabismus The condition when accompanied by the typical posture shuffling gait tremors mask like facies and rigidity is easily diagnosed. One should note the patient as he undresses and walks toward the examiner for the automatic movements of the upper extremities which normally accompany

walking, are usually lost In some cases, they are not abolished but when the patient comes to a standstill the arms will be drawn up slightly in flexion and he may shift his weight back and forth from one foot to the other Monotony of speech slight tremor of the hands, sighing or a slight irregularity in breathing may be observed There may be a reversal of the Argyll Robertson pupil (reaction to light but not to accommodation) If the patient tries to wink rapidly the eyelids tend to lag after one or two winks If the forehead is tapped gently with a percussion hammer the eyelids go into spasm Attempts to touch repeatedly his forefinger with his thumb result in 'freezing" of the two digits

Treatment There is no specific for this disease, symptomatic treatment to make the patient more comfortable is all that is possible The standard treatment today is the use of the hyoscine series of drugs such as *pellets* of *stramonium leaves* grains $2\frac{1}{2}$ three times daily or *hyoscine* tablets grain $\frac{1}{150}$ three times daily Both drugs are given until toxic signs appear The present trend in treatment appears to be the utilization of extracts of the belladonna root though the superiority of the belladonna groups of drugs has not been wholly established *Wine of Bulgarian belladonna* is given in ten drop doses after meals which are increased by five drops daily to the point of tolerance Unpleasant symptoms are often lessened by giving pilocarpine grains $\frac{1}{8}$ three times a day by mouth *Benzedrine sulfate* is useful for tics and oculogyric crises, it is given by mouth in ten milligram doses Myerson and Loman report a remarkable response of torticollis to large doses They have advised 20 to 30 mgm three times daily *Scopolamine hydrobromide* was given grain $\frac{1}{75}$ to grain $\frac{1}{200}$ with each dose to counteract the central over stimulation by the benzedrine *Atropine sulfate* has been used with good results by some It is started at $\frac{1}{60}$ grain three times daily and increased by $\frac{1}{150}$ grain twice daily until maximal therapeutic effects or toxic disturbances have resulted It can also be given in a 0 5 per cent solution Using a standard dropper delivering 1 minim per drop a small person is started with one drop a patient of average size with two drops and one above average with three drops three times daily The dose is increased by one drop three times a day at three day intervals until six drops are being taken at each dose, thereafter, the dose is increased at weekly intervals and with greater caution until 10 drops are being taken three times daily In warm weather the dose will have to be reduced by about 50 per cent It should be given at 8 A M , 3 P M and 10 P M

CHOREA—SYDENHAM'S CHOREA—ST VITUS DANCE

Chorea is a symptom resulting from a disturbance of the extrapyramidal system and is always due to infection usually, by a definite organism It is definitely related to tonsillitis, rheumatism and endocarditis It is a disease of early life, being most common between five and fifteen years Sometimes the disease may appear after scarlet fever or diphtheria, and less frequently after chickenpox Chorea may occur during pregnancy generally in primipara It is seen most frequently in girls and generally in the spring and summer months It is characterized by random twitchings, incoordination weakness facial contortions speech disorders irritability, psychic disturbances anemia diminished deep reflexes tonic reflex (in eliciting the knee jerk the foot stays up for a second or two before dropping back) and dilated pupils The average attack of acute chorea lasts for two or three months If the condition lasts longer it may not be Sydenham s chorea

Signs and Symptoms The onset may be gradual or set in acutely The child becomes irritable and unruly the movements become clumsy and awkward things are dropped from the hands and if the affection began in the lower extremity the gait is unsteady the legs being flung aimlessly about Next follows a generalized motor agitation the patient cannot stay quiet There are constant jerky movements referable to all muscle groups and without aim or purpose There are facial grimacing changes in mood and dysarthric speech As the condition grows worse the muscular movements may be so violent as to fling the patient out of bed Psychotic manifestations may appear and run the gamut from depression and hallucinations to acute mania and delirium If the movements are limited to one side of the body the condition is called

hemichorea The movements are usually accentuated by emotion or by being observed by others The writer has seen them cease temporarily after a stern command The *deep reflexes are diminished and may be absent* in the paralytic form The superficial reflexes are present There are no pupillary changes nor alterations in the visual fields or fundus The pulse is rapid and the fever usually high Changes in the spinal fluid are slight and inconstant

Diagnosis The diagnosis is fairly simple *Acute epidemic encephalitis* may be associated with choreic movements but the meningeal and root signs, and the pupillary and cranial nerve anomalies point to the correct diagnosis *Hysteria* should not be confused with chorea for hysterical movements are more purposeful and voluntary and there is no fever It will also be noted that in falling the hysterical patient does not hurt herself In general choreiform movements occurring in a young person usually a female with a history of rheumatic fever or evidence of a cardiac disorder point to Sydenham's chorea It is *differentiated from Huntington's chorea* by the absence of familial incidence and the fact that the latter usually occurs in middle life between 30 and 50 years

Treatment The treatment is directed toward keeping the patient quiet and comfortable and preventing sequelae such as heart disease Removal from school in the case of children many hours rest in bed in a darkened room with visitors excluded and the administration of mild sedatives such as bromides or chloral are indicated

In the more acute cases it may be necessary to pad the sides of the bed in order to prevent injury Tepid sponge baths are nearly always soothing and in some cases a wet pack of the whole body for hours at a time has a most quieting effect When rheumatism or endocarditis is present *salicylates* are said to be useful although no studies have shown them to be of direct value in chorea Arsenic or *nirvanol may do harm No special diet is* indicated in chorea *Hyperpyrexia* appears to be the best treatment Formerly typhoid vaccine intravenously was used beginning with 0 05 or 0 1 c c , the subsequent dosage being determined by the intensity of the reaction A much better form of treatment today is the *hypertherm* since it causes less discomfort The fever is raised to between 104° and 106°F (40° to 41°C) for periods of two hours every *other day Usually the chorea subsides in* from one to two weeks Cardiac involvement does not contraindicate fever therapy *Intravenous pentothal* may be needed in severe cases to quiet the patient as well as to permit intravenous feedings with glucose All agree that foci of infection should be sought and when possible eliminated

Circulatory Disturbances of the Brain

CEREBRAL HEMORRHAGE

Cerebral hemorrhage may be extradural subdural, subarachnoid or intracerebral The first three types mentioned are usually the result of trauma The chief cause of intracerebral hemorrhage is a rupture of an arteriosclerotic artery in one suffering with arterial hypertension If the vessel wall is atheromatous a normal blood pressure may cause it to rupture The attack usually comes on while the subject is under strain The onset is always sudden It may take place during sleep excitement or exertion Cerebral hemorrhage is rare in young adults it is more common in elderly patients Males are affected more than females and there seems to be a familial tendency The older the patient is there is less likelihood of hemorrhage and more likelihood of cerebral softening or thrombosis Although any region of the brain may be the site of hemorrhage the corpus striatum and the corona radiata are most often affected *The vessel is most often one of the lenticulostriate vessels*

Symptoms

The onset of symptoms is generally rapid although there may be some premonitory symptoms such as aphasia weakness or paresthesia slight numbness on one side of the face hand or arm Loss of consciousness is the *rule except in very small hemorrhages* Vomiting headache and convulsions are common There may be giddiness loss of speech and then a gradual loss of consciousness The patient may fall to the ground without any warning whatever Immediately following the

hemorrhage the respirations may be irregular and the pulse slow Symptoms and signs of importance besides those already mentioned are

1 Stiff neck or positive Kernig sign
2 Pupils dilated on the paralyzed side
3 Conjugate deviation of the head and eyes
4 Bilateral Babinski
5 Progression of focal neurological signs
6 Leucocytosis over 12,000
7 Spinal fluid pressure is usually over 350 mm of mercury
8 Spinal fluid is bloody
9 Sudden death may supervene
10 Stertorous breathing
11 Weakness of the corners of the mouth
12 Loss of abdominal reflexes
13 Flaccidity of the extremities

The following symptoms and signs are characteristic of hemorrhage as opposed to cerebral thrombosis or embolism

1 Loss of consciousness which deepens till a profound coma with stertorous breathing is reached
2 Congestion of the face and neck
3 A hard pulse with a rising blood pressure
4 Rapid appearance of fever and respiratory paralysis

Signs and Symptoms of Impending Cerebral Hemorrhage

It has recently been shown that a clinical study of individuals dying from essential hypertension may indicate a picture peculiar to those patients who are liable to have apoplexy Patients in the series who died of cerebral hemorrhage presented concurrent findings that were uncommon among other patients with essential hypertension Five signs and symptoms were consistently observed These were (1) severe occipital or nuchal headaches (2) vertigo or syncope (3) motor or sensory neurological disturbances (4) nosebleeds and (5) retinal hemorrhages in the absence of papilledema or retinal exudates It was concluded that the demonstration of any four of these manifestations in persons with essential hypertension warrants the assumption that death from cerebral hemorrhage will occur within 0 8 to 5 years (average 2 1 years)

Symptoms Suggesting Cerebral Compression

At first there will be a clouding of the sensorium associated with headache, mental dullness, insomnia restlessness confusion, delirium, stupor and coma if the compression is great As the compression increases the following will be noted slowing of the pulse increase in the blood pressure, irregular breathing and choking of the optic disk As the coma deepens there will be respiratory paralysis rapid pulse and a drop in the blood pressure

For the *differential diagnosis of coma*, the reader is referred to page 686 Besides the various conditions producing coma the following vascular lesions listed under the differential diagnosis of hemiplegia should be considered See page 943

Treatment of Cerebrovascular Accidents

Immediate treatment of the apoplectic attack is rest in bed with the head slightly raised The patient must be kept quiet and rest is essential This may be secured by the administration of *magnesium sulfate* 2 to 4 c c of a 25 per cent solution intramuscularly at intervals of two hours or by the careful administration of *morphine* or the *barbiturates* *Chloral hydrate* 25 to 30 grains in 8 ounces of milk, or other fluid per rectum may be efficacious Venesection is still practiced but only if congestive heart failure is present When it is employed at least from 200 to 300 c c of blood should be withdrawn For the relief of increased intracranial pressure intravenous administration of concentrated sucrose solution or magnesium sulfate may be given and may aid in lessening the cerebral damage Spinal punctures should not be performed except for diagnostic purposes Elimination must be maintained through the bowels and kidneys Catheterization is usually indicated If the patient is able to swallow fluids are permitted by mouth otherwise parenteral fluids are administered 1500 c c of normal saline under the skin and 1000 c c of 5 per cent glucose intravenously being the daily requirement

Restraints may be needed to keep the patient from thrashing about Side boards should be ordered if these patients are hospitalized Give an enema when necessary An ice cap

to the head can do no harm and it may do some good by diminishing the blood flow Tube feeding may be necessary if coma persists for more than 24 hours Dietene (Dietene Co, Minneapolis Minn) is an excellent product for this purpose Frequent turning of the patient is necessary to prevent decubitus ulcer Close nursing attention may be necessary in some cases to keep the bed linen dry and to prevent strangulation or aspiration A retention catheter is frequently required Care should be taken to avoid burns by heat pads or hot water bottles If syphilis is present or if the cause of the thrombosis is syphilitic endarteritis the patient should be treated as for vascular neurosyphilis providing his age is no contraindication If thrombosis or embolism is suspected *do not resort to venesection* When recovery has begun and the patient is able to cooperate attention should be directed toward the restoration of muscle function by massage and physiotherapy This consists of light massage of the muscles and passive movements of the affected limbs The patient must be encouraged to use the paralyzed muscles With any tendency to contracture splints should be used Electricity is of no value Simple exercises such as squeezing a rubber ball or sponge touching the fingers one after the other in rotation, or larger movements coordinating both arms are of value These exercises should never be carried out to the point of fatigue Subdeltoid bursitis can be avoided by active motion of the arm at the shoulder joint Baking massage and fixation of the joint are not indicated A gradual increase in the active motion of the joint should be insisted upon such as the use of a wheel chair attendant assistance in walking, or the use of a cane

Second hemorrhage may be expected Excitement worry overeating alcohol and strong coffee should be prohibited and where possible the patient s life and social problems should be planned for him

Neostigmine Therapy of Hemiplegia and Facial Paralysis

Kabat (46) reports the treatment of hemiplegia with neostigmine and atrophine administered subcutaneously once or twice daily The drug was found to depress muscle tonus and thereby relieve spasticity, increase range of passive motion and decrease deformity There was also relief from muscle pain and definite increase in the power of voluntary motion Improvement was evident in some cases within 24 hours after initiation of therapy

In the same report (46) the drug has been shown to be of benefit for facial paralysis, dysphonia, dysarthria and dysphagia Recovery of function following cerebral infarction usually is attributed to the formation of new pathways and the taking over by other areas of the brain of the function of the region destroyed Cholinergic facilitation at synapses may conceivably accelerate the formation of new pathways in the central nervous system The possibilities of neostigmine therapy will be distinctly limited as the drug can only improve function within the limits imposed by the irreversible brain damage and the possibilities for formation of new neural pathways to the abnormally functioning motor units

Since the localization and extent of the lesions will vary from case to case there will be no uniformity in the results obtained with the drug To quote Kabat The most that one can hope for is that neostigmine therapy may perhaps result in full and efficient utilization of the remaining central nervous tissue and thereby make it possible to bring about maximal functional recovery

Dosage 2 c c neostigmine methylsulfate, 1 2000 solution (*Prostigmine—Hoffman—La Roche Inc*) is injected subcutaneously once or twice daily *Atropine sulfate*, grain 1/100 (0 65 mg) or grains 1/150 (0 43 mg) is injected at the same time and is used to eliminate the unpleasant side-effects of the neostigmine

THE DIFFERENTIAL DIAGNOSIS OF HEMIPLEGIA

Although denoting a paralysis of one half of the body hemiplegia is commonly used to include all cases of paralysis or weakness of the arm and leg on the same side in addition the face may be affected either on the same or opposite side of the body in which case the term crossed or alternating paralysis is used Cases of hemiplegia certainly represent one of the commonest forms of diseases of the brain which the general practitioner is liable to

encounter In practice, the vascular lesions of the brain are the most common causes of hemiplegia and it is to these that particular attention will be directed

The vascular lesions of the brain responsible for the great majority of cases of hemiplegia are as follows

1 Arterial obstruction with resultant cerebral softening due to *cerebral embolism*, or *cerebral thrombosis*
2 Vascular lesions in the internal capsule
3 Cortical lesions
4 Sub cortical lesions
5 Thalamic lesions
6 Crus Cerebri lesions
7 Pontine lesions
8 Lesions of the medulla
9 Lesions of the spinal cord

Cerebral Embolism

A cerebral embolus may occur at any age Some sources of emboli are blood clots within the circulation such as those contained in an aneurysm, an atheromatous ulcer of a blood vessel thrombi in a fibrillating auricle, vegetations of ulcerative endocarditis thrombosis of a pulmonary vein and fat emboli following fractures If the embolus is infected, a cerebral abscess or meningitis may ensue

Symptoms The symptoms are abrupt and somewhat similar to those of cerebral hemorrhage but loss of consciousness is not as common Convulsions may occur headache is common If the capsular artery is affected hemiplegic signs will appear

Treatment Rest and the general measures for the treatment of cerebral hemorrhage are employed If there is an infection such as thrombophlebitis or endocarditis the sulfonamides may be of value When the infection is meningeal frequent lumbar punctures or penicillin may be required In the event of a brain abscess, surgical intervention is necessary

Cerebral Thrombosis

In elderly individuals with arterial hypertension the thrombosis is usually on an arteriosclerotic basis In younger adults it is usually on the basis of a syphilitic endarteritis In other instances where there is a condition of blood stasis and as a result the brain gets a lessened supply of blood, a physiologic thrombosis may result which may cause hemiplegia and coma persisting for days

Symptoms There may be dizziness, nervousness, headache, increasing weakness on the contralateral side and coma The symptoms may resemble those of hemorrhage

Treatment There is little difference in the treatment of thrombosis and hemorrhage Stimulants are useful and in those with a known arterial hypertension, it is better not to attempt to lower the blood pressure by cardiac depressants

Vascular Lesions in the Internal Capsule

Hemorrhage into the internal capsule is shortly followed by a complete flaccid paralysis of the limbs on the opposite side of the body A conjugate deviation of the eyes toward the paralyzed side may be observed at the onset The tendon reflexes are diminished or absent on the affected side during the early stages, the plantar reflex is extensor in type Later during recovery, the tendon reflexes return and become exaggerated and the limbs which were paralyzed begin to show signs of rigidity or spasticity The more severe the initial lesion in the brain the longer is spasticity delayed The typical picture of residual spastic hemiplegia is that of the arm held stiffly to the side of the body, adducted at the shoulder joint, semiflexed at the elbow and with a tendency to flexion with contractures of the fingers and wrist The leg is rigid in extension This paralysis is the supranuclear type in which the upper part of the face is less affected than the lower portion The movements of the paralyzed side of the face are generally normal in response to emotion The tongue may be deviated towards the paralyzed side of the body The face usually recovers first then the lower extremity while the residual paralysis of the arms is the more persistent When recovery has reached its maximum it will be noted that the finer movements of the fingers are more affected than the larger movements which occur at the elbow and shoulder joint Other signs are slow and stertorous respiration a slow pulse a flat nasolabial fold on the paralyzed side and usually incontinence of urine and feces

Cortical Lesions

A monoplegia is more likely with a cortical lesion owing to the wide distribution of the motor centers If a hemiplegia is present at the onset the residual paralysis usually becomes localized to one limb or to one side of the face and arm Convulsions are not uncommon with cortical lesions Thromboses are more common in the cortex than are hemorrhages and, aphasia is likely to be associated with thrombotic lesions of the cortex of the left cerebral hemisphere We can conclude that a hemiplegia resulting from a cortical lesion is less severe and is associated with less spasticity than that resulting from a vascular lesion of the internal capsule

Sub-Cortical Lesions

The paralysis is more extensive and more likely to be complicated with hemianesthesia from involvement of the thalamo-cortical sensory fibers In particular tactile discrimination localization and position sense are disturbed If the optic radiations are involved a crossed homonymous hemianopia is produced with loss of visual fields on the side opposite to the lesion

Thalamic Lesions

The following are characteristic of thalamic lesions

1 Hemi ataxia
2 Hemi anesthesia
3 Spontaneous pain in the affected limbs
4 Over reaction to stimuli such as a scratch or a pin prick

Crus Cerebri Lesions

Weber's Syndrome This is characterized by a fixed dilated pupil ptosis external strabismus on the side of the lesion and hemiplegia on the other side

Benedict's Syndrome The lesion extends into the tegmental area of the crus it involves the red nucleus and produces in addition a tremor or ataxia of the extremities

Pontine Lesions

Upper Pontine Lesions There will be paralysis of the face and limbs on the same side of the body and on the side opposite to the lesion

Lower Pontine Lesion Various crossed hemiplegias are produced Usually a peripheral type facial paralysis is present on the side of the lesion and the nucleus of the 6th nerve may be affected producing a 6th and 7th nerve paralysis on the side of the lesion and paralysis of the arm and leg of the opposite side

Lesions of the Medulla

While not common a lesion near the midline may produce a unilateral paralysis of the tongue on the same side with a crossed paralysis of the limbs Lesions more laterally placed will produce in addition a unilateral paralysis of the palate and vocal cord on the side of the lesion Horner s syndrome, analgesia in the area of the fifth nerve and ataxia of the limbs In addition, there will be a loss of pain and temperature sense in the trunk and extremities on the opposite side of the body

Lesions of the Spinal Cord

Spinal hemiplegia may occur from a unilateral lesion of the cord below the medulla and above the 5th cervical segment The paralysis is on the same side as the lesion

Other Causes of Hemiplegia

Less common causes of hemiplegia are

1 Birth injuries
2 Congenital malformations of the brain
3 Encephalitis
4 Meningitis
5 Sinus thrombosis
6 General paralysis of the insane
7 Cerebral tumors and abscesses
8 Traumatic hemorrhages
9 Disseminated sclerosis
10 Paralysis agitans
11 Chorea
12 Hysteria

Cerebral Tumors In cases of gradual onset of hemiplegia cerebral tumor must be considered even in the absence of headache vomiting and papilledema as with a slowly growing tumor these signs may be absent for some time after definite manifestations of local brain disease has been observed

Paralysis Agitans Paralysis agitans may begin with a hemiplegic distribution When the symptoms consist of rigidity and lack of movement without the characteristic tremor

as is often the case in early stages, the patient may present himself as an obscure form of hemiparesis, without the accompanying pyramidal tract signs such as the extensor plantar reflex

Paralytic Chorea In this uncommon type of chorea, the paralysis is nearly always hemiplegic, and the weakness of the limbs is associated with a hypotonia and flaccidity of the muscles and without any marked degree of muscular wasting or signs of pyramidal tract involvement This diagnosis is very easy to miss unless there is involuntary movement present and in severe cases they are generally absent in the paralyzed limbs

Hysterical Hemiplegia The paralysis is more often a flaccid type, the arm hangs loosely by the side of the body, and when walking is possible, the leg tends to be dragged behind the body like a useless appendage Sometimes, the patient appears to be unable to move the leg from the horizontal position when he lies down Signs of pyramidal tract disease are absent With the patient lying flat on his back and his arms crossed over the chest, he is told to sit up without using the arms to help himself In hemiplegia of organic origin, the paralyzed leg tends to be raised in the air with some flexion of the hip In hysterical cases the apparently paralyzed leg is kept firmly pressed down on the bed Hysterical hemiplegia generally spares the face, tongue and platysma In organic hemiplegia the platysma is always affected True hypertonus does not exist and if contractures exist they can usually be overcome during anesthesia Not infrequently hysterical hemianesthesia exists See figure 169

Cerebral Arterial Spasm

While it has not perhaps been proved conclusively that this occurs such a diagnosis seems to be substantiated in certain cases Acute hemiplegias monoplegias and other phenomena are frequently seen in the absence of demonstrable cerebral disease The rapid and transient nature of such phenomena also make it highly probable that they are caused by temporary spasm of the vessel rather than by a pathologic condition like embolism or thrombosis Again, certain cerebral symptoms appear to respond to vasodilators such as *amyl nitrite* and *nitroglycerin* Such symptoms in the aged, suggest cerebral arteriosclerosis and may forebode thrombosis

Symptoms There is no definite clinical picture It may vary from a moderate headache, mild numbness of the face, arm, or leg, or mild visual defects to complete hemiplegia Consciousness may or may not be affected Incontinence may occur, in addition to aphasia and other apoplectic phenomena The patient usually recovers rapidly, often while awaiting medical aid Recurrent attacks are common, although isolated attacks are frequently seen

Treatment *Amyl nitrite* inhalation or *nitroglycerin* grain $\frac{1}{100}$ hypodermically are often of benefit *Rest* is important and sedation can be brought about by the use of *luminal* grains $\frac{1}{2}$ three times daily, or *sodium bromide* grains 15 three times daily Reassurance benefits the patient and is well worth the time spent

Cerebral Arteriosclerosis

This is a condition of late mid life or old age and is caused by the progressive sclerotic changes in the cerebral arterial system It may occur without either hemorrhage or thrombosis but usually the symptoms are the result of small thromboses affecting various parts of the brain Cardiorenal disease and hypertension may or may not be present The commonest site of vascular involvement is the *middle cerebral artery* and its branches

Symptoms and Signs Symptoms are the result of partial blocking of vessels which in turn leads to impairment of cerebral function This is manifested by a progressive reduction in the intellectual capacity and impaired memory especially for recent events and, emotional instability Constructive ability is lost and as the disease progresses it leads to dementia and an almost vegetative existence *Common early symptoms* are headache vertigo insomnia irritability and euphoria Epileptic attacks may occur, with aphasia hemianopia or hemiplegia often disappearing within a few hours Hemiplegia is frequent and is usually sudden in onset following such incidents as straining at stool heavy lifting or some sudden exertion An apoplectic seizure may occur sud

denly and is the sequel of cerebral hemorrhage In some patients there may be premonitory symptoms such as a sense of dizziness or pressure in the head anxiety confusion thickness of speech hemiparesthesia and epistaxis or retinal hemorrhage may also precede the acute attack. The acute attack is ushered in by loss of consciousness which may be slight or it may be a deep lengthy coma It is usually accompanied by urinary incontinence and respiratory irregularity as well as a depression of both the blood pressure and the pulse rate There may be only a transient vertigo Bleeding into the cerebellum and pons is less frequently associated with disturbances in consciousness There is a characteristic appearance of the patient during the acute attack The face is flushed and has a puffy appearance the pupils may be normal in size or dilated but they are fixed and the corneal reflexes are both absent The cheeks are puffed out, more so on the paralyzed side and breathing is slow noisy and deep The pupil on the side of the lesion may be dilated and if there is conjugate deviation of the eyes the hemorrhage is usually situated on the side toward which the head and eyes are directed During this stage a *lumbar puncture* will reveal an increased intracranial pressure and the presence of blood in the cerebrospinal fluid If the hemorrhage enters the lateral ventricles the patient s coma will deepen and there will usually be found signs of bilateral paralysis of the body Hemorrhage into the pons may give rise to crossed paralysis that is weakness of one side of the face and of the opposite arm and leg

Unless the patient dies consciousness gradually returns the reflexes return then become hyperactive Babinski s sign may be present on the affected side and spasticity usually sets in If the patient has been unable to swallow he can now and there is some return of voluntary movement The patient presents a characteristic look there is marked facial asymmetry with some sagging of the angle of the mouth on the affected side the palpebral fissure is wider than normal the nasolabial fold is less marked and the patient drools on the paralyzed side Bloody spinal fluid is not as common in cerebral arterial thrombosis as it is in cerebral hemorrhage the onset is usually not as abrupt stiffness of the neck is not so frequent, and Babinski s sign is not so often present

In cerebral arteriosclerosis impairment of vision is common and arteriosclerotic vessels may be seen in the retina Multiple small foci of softening may produce the syndrome of pseudobulbar paralysis This syndrome is characterized by a small step gait salivary drooling and difficulty in mastication phonation and deglutition In chronic cerebral arteriosclerosis when the arteriosclerotic changes have affected the basal ganglia and the extrapyramidal system the syndrome of Parkinson s disease appears

The course of cerebral arteriosclerosis is downhill but occasionally there are long remissions The eventual *prognosis* is bad and death usually results from cerebral thrombosis or an intercurrent infection It must be remembered that in this disease the judgement is impaired and many capable men play havoc with their resources before the disease is recognized

Treatment. There is no specific treatment for this condition The most effectual form is psychotherapy with encouragement and reassurance The patient should have freedom from responsibility and protection from the possibility of becoming aroused or angry Reasonable limitation of activity should be recommended but this does not mean that the patient should be made to feel like a chronic invalid for the balance of his days Hobbies are recommended and graduated exercises are beneficial In the severe types complete cessation of work will be necessary *Potassium iodide* in doses of 0 15 c c (3 minims) to 0 25 c c (5 minims) of the saturated solution is usually administered The epileptic attacks are controlled by luminal Alcohol tobacco and coffee should be limited As the patients deteriorate they will be best cared for in hospitals or rest homes and when their judgement becomes impaired a guardian should be appointed to protect their property Restlessness is treated by luminal giving small doses of $\frac{1}{4}$ to 1 grain after meals They should be warned against straining at stool and against excess sexual indulgence The meals should be small and taken with as little fluid as possible The bladder and bowel functions should be supervised carefully

The Dementias

Senile Dementia

Senile dementia is a gradual process characterized by progressive intellectual enfeeblement beginning usually with a loss of memory for recent events, lack of impressionability and the ability to recognize faces There is an alteration in the patient's personality, he is easily irritated and becomes grouchy and egotistical, he may have delusions of persecution or of the infidelity of his wife As the years go on he may not countenance the slightest deviation from the usual order of things He may hoard and become quarrelsome He seems to live in a former day showing a marked tendency to reminiscences As the condition becomes progressively worse judgement fails and initiative is lost the patient leading a more or less vegetative existence

Alzheimer's Disease

This is a fairly rapid progressive dementia occurring earlier than the senile dementias It is characterized by apraxia and aphasia associated with a marked dementia There may be epileptiform attacks There is a pronounced defect of memory and complete disorientation The disease occurs at about fifty years of age and the patient survives generally for two or three years

Pick's Disease

This disease like Alzheimer's disease is considered as an early form of dementia Only about eighty cases have been described It occurs more commonly in women and its progression is rather slow Its onset is somewhat later than that of Alzheimer's disease It is characterized by *emotional dullness* and the *loss of initiativ ethical sense* and *mental capability* There is mental enfeeblement though memory is fairly well preserved Aphasia apraxia and agraphia are common, the dementia advances and the patient finally becomes mute incontinent cachectic and vegetative Encephalography reveals some internal hydrocephalus and focal collections of air over the cortex Death occurs in from five to ten years

Prognosis and Treatment There is no successful treatment for the senile and arteriosclerotic forms of dementia An early diagnosis is of the utmost importance because it is in the early stages that the patient may commit serious errors of judgement Long before his irresponsibility has been noticed by relatives or friends, early paranoid ideas may lead to unwarranted alterations of a will or erroneous judgement may lead to unwise investments and the frittering away of the savings of a lifetime Early diagnosis, however is very difficult, for it is usually well along in the disease before the suspicions of relatives are aroused to the point of seeking medical advice The relatives are unwilling to see anything wrong in the patient's attitude or behavior He is considered as being "ornery" or "cantankerous" It is true that most patients can be managed at home with the help of a maid or a companion and no one will disagree that such an arrangement is preferable to an institution The doctor will do well to weigh carefully the home conditions and the real attitude of the relatives who may seek advice from the doctor Many old people who are entirely harmless lead anything but peaceful lives and suffer many insults and torments at the hands of callous indifferent children or grasping sons and daughters in law Many of these cases would do much better in institutions or homes for the aged If need be the children of such people should be made to see their obligation and contribute jointly to the maintenance of the patient in a suitable home or institution The physician should never allow himself to be swayed by unscrupulous relatives or in laws who desire to commit an aged person merely because he is 'in the way' or is queer One should have a proper regard and respect for the idiosyncrasies and individual peculiarities of these old people

Aged patients react more violently to drugs than younger people and it is well to avoid sedatives when possible since they confuse and befuddle even normal people Sedative warm baths and warm drinks at bedtime will serve the purpose more satisfactorily A well balanced diet supplemented with vitamins should be supplied Alcohol except in small amounts is contraindicated a glass of ale or beer may serve as an excellent stimulant to the appetite

Cerebral Aneurysm

Cerebral aneurysm may be due to congenital defects embolus or, in some cases to trauma

Aneurysmal dilatation is more frequent in the cerebral vessels than in the other arteries of the body with the exception of the aorta The arteries at the base of the brain are most commonly involved The lesions are more frequent on the left side They are usually asymptomatic until rupture occurs when paralysis suddenly appears affecting as a rule, the third cranial nerve There is a sudden excruciating headache loss of consciousness and marked nuchal rigidity The deep reflexes are usually absent Later, the eye grounds may show edema and venous engorgement A lumbar puncture will reveal a large amount of free blood in the spinal fluid The site of perforation may be so small that there is slow oozing into the subarachnoid space When this occurs periodically it may give rise to meningeal irritation closely resembling that seen in pachymeningitis hemorrhagica Aneurysms lying in the sphenoid fissure may cause pressure on the optic nerve then paralysis of the extra ocular muscles and amblyopia result If the wall of the aneurysm is calcified roentgen examination may reveal its location Traumatic aneurysms of the carotid cavernous sinus type give rise to a unilateral pulsating exophthalmos and a systolic murmur heard in the temporal region Aneurysms of the anterior cerebral artery manifest themselves by unilateral optic atrophy and anosmia

Diagnosis The diagnosis of aneurysms of the cerebral blood vessels is extremely difficult and is usually made after death However sudden onset of coma with hemiplegic signs in young individuals without a history of hypertension or syphilis should make one consider the possibility of aneurysm The history of repeated attacks of meningeal irritation accompanied by a bloody or xanthochromatic spinal fluid is very suggestive of aneurysm The conditions to be ruled out are *hemorrhagic pachymeningitis ophthalmoplegia migraine* and *infectious meningitis* Tumors of the trigeminal nerve are sometimes confusing

Pachymeningitis Hemorrhagica This usually occurs in the middle age period and in the chronic psychoses chronic alcoholism and syphilis the chief signs are headache vomiting contracted pupils with a slow reaction to light and gradually increasing pareses and paralyses

Infectious Meningitis A lumbar puncture will clear up the diagnosis

Treatment The best treatment for ruptured aneurysm is rest An initial lumbar puncture is advisable to aid in diagnosis but the repeated withdrawal of fluid seems ill advised since the lowering of the spinal pressure may reopen the point of perforation with fresh hemorrhage Sudden death may follow jamming of the brain stem into the foramen magnum However if the signs of cerebral compression are severe lumbar puncture should be employed and later after the acute stage has passed and signs of meningeal irritation have appeared it may greatly relieve the severe headaches Should recovery follow the rupture of an aneurysm, another hemorrhage will probably occur at a later date and not uncommonly with fatal results The patient should be kept absolutely quiet in bed for from two to three weeks after the rupture and allowed to resume his duties gradually and in a modified form

Subarachnoid Hemorrhage

This condition occurs as the result of the rupture of small superficial cerebral vessels usually located on or close to the surface of the brain It is met with in the clinical course of some of the cerebral vascular diseases such as (1) congenital aneurysms (2) cerebral arteriosclerosis and (3) hypertension Some cases are ascribed to epidemic encephalitis

Signs and Symptoms The onset is usually initiated by a sudden severe pain in the occipital region and often follows or accompanies severe exertion Nausea, vomiting vertigo stiffness of the neck blurring of vision and weakness or paralysis of the external rectus muscle follow Paralysis of the extremities and sensory changes are rare The symptoms may persist for weeks Early in the course the superficial reflexes may be abolished and there may be hypertension and evidence of retinal arteriosclerosis A lumbar puncture will reveal frank blood which does not clot and if allowed to settle the supernatant fluid has a brownish tinge The pressure is usually definitely increased There is no change in the chlorides of the spinal fluid and its sugar and protein contents may be elevated

more frequently than males Seizures sometimes appear at the menstrual period in young girls, but the menses do not necessarily act as the exciting cause There is probably a tendency to convulsions, and the added strain of the menses tends to bring to the fore what is already present

Symptoms and Signs Epilepsy may be present in the form of grand mal or major attacks, petit mal or minor attacks 'equivalents,' or combinations of the three Premonitory symptoms may precede the actual warning of the attack These consist of dream states, starts and jerks, headaches flashes of light and giddiness The first phenomenon of the attack is the aura Aurae are chiefly sensory, but those from the pre central cortex are motor The aura is the first discharge that reaches a threshold level It is present in from 50 and 60 per cent of cases It may be unilateral, in one side of the tongue face trunk one arm or leg, bilateral as tremors, vagal or visceral as a sinking sensation in the epigastrium, choking dyspnea or nausea vertigo or sensations in the head special sense aurae like odors taste, ringing or hissing sensation smacking of the lips, moving figures or flashes of light

Grand Mal Seizure This is characterized by convulsions and while it may occur suddenly, in many cases an aura of sensory nature is present and in 50 per cent a cry may be heard In the convulsive stage the patient falls like a log making no effort to save himself, goes into a tonic convulsion, holds his breath becomes pale or cyanotic the pupils dilated or fixed the body hypertonic and rigid and the jaws tightly clamped In about twenty seconds the clonic phase begins The muscles of the body relax and contract rapidly The patient may chew his tongue or froth at the mouth, the eyes are partly open and the breathing is blowing in character the extremities and head may jerk and the patient lose control of his sphincters The superficial reflexes are usually lost and the deep reflexes diminished There may be a positive Babinski sign The patient slowly relaxes and a deep sleep or post epileptic stupor may last for hours after which the patient resumes his mental and physical normal state with little or no knowledge of what happened Headache is a common sequel The attack may be followed by states of automatism or furor

Petit Mal Seizure These attacks are characterized by sudden, brief periods of unconsciousness usually without an aura They last only a few minutes, the patient has no recollection of the episode but he does not fall There may be a few facial twitches, a dropped word an abrupt start, or a sudden incontinence of urine Whatever he is doing is broken off by the attack and he seems out of all contact with his surroundings

Epileptic Equivalents Epileptic equivalents are not only of clinical interest, but they have a medico-legal aspect as well The acts of a patient in a period of automatism may be illegal and there may be great difficulty in convincing the layman that such acts were not deliberate and intentional Emotional automatism is sometimes observed and during periods of post epileptic mania the patient may be insolent and abusive

Jacksonian Attacks Jacksonian attacks are produced by irritation of some part of the motor cortex There is no disturbance in consciousness and the patient is aware of the convulsion which is focal in type, either one or a group of muscles being involved The attack usually begins with a sensory aura followed by a tonic spasm and then by clonic jerking A fit starting in the toe may move to the foot, leg knee thigh, hip, shoulder, arm and hand and affect the face last of all There may be weakness of the affected part for some time after

Psychic Equivalent The patient has a mental equivalent of a fit without warning he forgets his identity and assumes another personality later returning to his normal state

Status Epilepticus This consists of a series of rapidly repeated convulsions during which the patient is usually unconscious and the stupor progressively increases, with an associated temperature rise resulting frequently in death of the patient from cardiac dilatation or pulmonary edema

Diagnosis of Epilepsy The diagnosis of epilepsy is sometimes very difficult The following measures may aid in the study of a suspected case

1 *History—this should stress the heredity* birth and developmental aspect with

careful attention to previous diseases and traumatic injuries
2 Careful physical and thorough neurological examination
3 Laboratory procedures
a) Roentgen study of the skull
b) Spinal puncture with careful examination of the spinal fluid and evaluation of the dynamics
c) Urine and blood analysis
d) Metabolic studies to rule out alteration of sugar or nitrogen metabolism
e) Electroencephalogram
f) Periodic examination to rule out the possibility of brain tumor

Differential Diagnosis One must consider and exclude the following
1 Hysteria
2 Narcolepsy
3 Pyknolepsy
4 Uremic convulsions
5 Eclamptic seizures
6 Strychnine convulsions
7 Tetany
8 Cerebellar or tonic fits
9 Psychotic episodes
10 Other causes of coma (See page 686)

Treatment of Epilepsy The immediate management of a patient in a grand mal seizure consists in protecting him from injury Measures to prevent or shorten the attack are useless The patient should be allowed to lie where he falls the clothing about the neck should be loosened and a soft object inserted between his teeth If the tongue obstructs the glottis the jaw should be held forward and the head turned to one side Following the convulsion the patient may be moved to a quiet place and allowed to sleep until he awakens The use of side boards to the bed may be advisable Usually the patient feels well in a few hours or even in a few minutes Children should be kept in bed for the remainder of the day

Status Epilepticus More active measures must be taken in status epilepticus *Sodium phenobarbital* can be given intravenously or intramuscularly in doses of 0 2 to 0 4 gm *Sodium amytal* may be given intravenously (slowly) in 0 5 gm doses *Paraldehyde* may be used as a rectal instillation in 8–12 c c amounts It may also be given intravenously in 1 c c doses in physiological saline Hypertonic *magnesium sulfate* (25 per cent) may be given intravenously It is rarely necessary to use ether anesthesia It is safer to continue the sedation with one drug rather than to change Care should be taken to avoid injury aspiration and over sedation Parenteral dextrose and fluids should be given as a rule if the status is prolonged *Lumbar puncture* may be done if required

Maintenance Dosage Most patients with grand mal, petit mal and psychomotor epilepsy are maintained on *phenobarbital*, the usual dose being 0 1 gm in the evening It may be necessary to give 0 05 gm during the day

Dilantin Sodium has been successful in cases not doing well with phenobarbital It may be used alone or in conjunction with phenobarbital It is more effective in grand mal and psychomotor seizures than in petit mal This amount must be determined by trial with each patient it varies between 0 2 gm and 0 6 gm daily Usually the dose is 0 3 gm in 24 hours It is given in 0 1 gm capsules *with or after meals* A sudden change from a previously established form of medication should be avoided since the mode of action of the new drug may be different and provoke status epilepticus A good plan is to continue the dose of the original drug for two or three days but to reduce it by 25 per cent each day

Toxic Effects of Dilantin Some patients experience mild stomach heaviness,' nausea and vomiting With severe nausea, 15 drops of dilute hydrochloric acid at the time that the drug is taken relieves symptoms 'Nervousness tremor of the hands, diplopia with nystagmus drowsiness and headaches may occur Usually the patients are relieved by a decrease or a more even distribution of the dosage Toxic dermatitis may occur, if it should the drug should be stopped at once If the skin reaction is mild the drug may be re administered If the skin reaction is severe or if toxic dermatitis recurs with re administration it is inadvisable to continue Hypertrophy of the gums occurs in a small percentage of patients usually children and young adults

Prognosis Convulsions of infancy which persist for 4 or 5 years may disappear and recur at puberty The prognosis is more favorable if the patient is of the female sex

and if the onset occurs after 20 years of age It is also better under the following conditions short duration of the disease and an hereditary taint, long intervals between fits, and occurrence of the seizures in either the waking or the sleeping state but not in both Minor attacks are arrested with difficulty Cases that can not tolerate medication do rather poorly

General Measures Constipation is to be avoided and a diminution in the amount of meat eaten has been found by some to be of some empirical value Alcohol swimming working near moving machinery or in hazardous pursuits should be prohibited Peace of mind regular exercise and sleep are important treatment Needless to say, epilepsy due to neoplasms is a surgical problem

Injuries to the Brain

EXTRADURAL HEMORRHAGE

In a recent excellent paper (25) Huston Merritt has pointed out that the studies on extradural hemorrhage all emphasize the fact that the classical symptoms or syndrome (unconsciousness after an injury a lucid interval and relapse into coma) is present in less than 50 per cent of cases Consequently, this type of hemorrhage is often not recognized which has resulted in an unduly high mortality rate Severe damage to the brain may be a factor in the absence of the lucid interval To quote Merritt

> The development of hemiplegia or a dilated fixed pupil should lead to suspicion of the presence of an extradural hemorrhage This is one condition in which an emergency roentgen examination is important *A fracture line in relation to one of the branches of the middle meningeal artery or one of the large venous sinuses is confirmatory information for the diagnosis* While extradural hemorrhage may follow a relatively minor injury it is doubtful whether it ever occurs without fracture of the skull although occasionally such fracture may not be demonstrable by roentgenogram
>
> Increased intracranial pressure as measured by lumbar puncture is helpful in the diagnosis but hematoma can be present even when the pressure is normal Blood in the spinal fluid may or may not be present depending on the presence or absence of associated injury to the brain With subdural hematoma the hemiplegia is occasionally on the same side as the extradural hemorrhage It is commonly assumed that all extradural hemorrhage is due to rupture of a meningeal artery but it has been shown that in a large portion of cases the bleeding is from the venous sinuses *If the diagnosis is made promptly and the patient is immediately treated by removal of the clot by operation* the mortality rate should be less than 25 per cent

SUBDURAL HEMATOMA

The diagnosis of acute subdural hematoma is frequently difficult It is usually the result of rupture of one of the veins which bridge the subdural space and should be suspected in any case of head injury when the patient does not respond in a satisfactory manner to adequate treatment, when neurologic signs develop or when the state of consciousnes fluctuates There may be hemiplegia on the same side as the hematoma and since the hematoma may be bilateral in a small percentage of cases it is advisable to explore both hemispheres with burr holes when this diagnosis is suspected The cerebrospinal fluid pressure may either be elevated or normal It usually contains blood owing to concomitant cerebral damage The prognosis is not as favorable as for extradural hemorrhage owing to brain damage being more frequent and often more severe

Chronic subdural hematoma should be suspected in a patient with a history of a recent head injury or in an alcoholic who may have had an injury without remembering it The clinical picture is similar to that of an expanding intracranial lesion such as brain abscess or tumor

INJURIES TO THE CRANIAL NERVES

The cranial nerves are frequently damaged in head injuries The *olfactory nerve* is probably the most commonly damaged followed in order by the VIII VII VI and II cranial nerves It should be remembered that blows in the occipital region may cause injury to the olfactory nerve Taste may be impaired with the olfactory sense and is explained by the fact that smell is an important element in the sense of taste Actual severance of the optic nerve is uncommon The development of visual defects following head injury has been explained as being due to the development of *perichiasmal arachnoiditis* Fractures of the temporal bone may cause injury to the facial nerve The onset of facial paralysis may be delayed until several days following the injury

as a result, presumably, of hemorrhage around the nerve The prognosis is good In damage to the VIII nerve hearing may be impaired and may be either of the nerve or middle ear type If the labyrinth is injured, vertigo may persist for a long time Not uncommonly Meniere s disease develops at a latter date

EPILEPSY FOLLOWING HEAD INJURIES

Epileptic seizures may develop either within a few hours following head injuries or not until several years has elapsed, it is then difficult to evaluate the role of the injury in the etiology of the epileptic seizure These seizures may be of any type except petit mal and contrary to the usual impression as Merritt has pointed out (26) they are more often generalized than Jacksonian The prognosis for remission of the attacks is better if they develop within a few days or weeks of the injury than if they appear months or even years later The more severe the injury the greater the likelihood that seizures will result There is no evidence in the literature that the retention of a deeply situated foreign body predisposes to the development of epileptic attacks

Treatment is both medical and surgical the latter consisting in the removal of car tissue Operation is indicated when a localized abnormality of the cortex can be demonstrated by electroencephalography or by the injection of air

POST TRAUMATIC CONCUSSION AND POST TRAUMATIC PSYCHONEUROTIC STATES FOLLOWING INJURIES TO THE HEAD

In recent years there has been a constantly increasing number of claims for awards in cases of head injuries caused by industrial, war and automobile accidents These claims have been based upon compensation laws and on public liability It therefore follows that the economic importance of a proper understanding of the physical as well as of the mental effects of such injuries is of the greatest importance both from the viewpoint of recovery and of occupational disability The legal attitude as to responsibility for personal injury adds to the complexity of the subject In order to secure compensation an attempt is made in the courts to magnify the extent of injury to the patient, who often over emphasize trivial symptoms From the neurologic standpoint, there is an increasing tendency to attribute many organic disea es to a previous injury to the head or spine the claim often going beyond the bounds of logical deduction and pathological verification

CLASSIFICATION OF HEAD INJURIES

Head injuries may be classified as organic or functional dependent upon the presence or absence of structural changes in the nervous tissue

Organic Injuries

Brain pressure from depressed skull fracture
Epidural hemorrhage
Subdural hemorrhage
Lacerations
Contusions
Softenings
Infectious sequelae, i e meningitis abscess

Functional Disorders

Post traumatic psychoneuroses
Traumatic hysterias
Psychogenic states

Schaller believes (27) that midway between these two contrasting states is the post traumatic concussion state variously designated as traumatic encephalopathy traumatic encephalitis, cerebral neuresthenia, post traumatic head syndrome, punch-drunk ' or concussion neurosis

THE EFFECTS OF TRAUMA

Trauma may produce mental symptoms in two ways It causes either structural injury to the brain or emotional disturbances which n one form or another are prolonged for some time In the first case the mental reaction is of the organic type, often with certain more subtle changes of temperament or personality, in the second the result is u ually a psychoneurosis In the first group, the head has been injured either directly or indirectly in the second the seat of injury may be anywhere or nowhere The first group is usually called ' traumatic psychose , the second, traumatic neuroses '

The physical effects of brain injury are both focal and diffuse immediate and delayed The focal lesions consist, at first, of tissue destruction, hemorrhages and edema and later, in secondary degeneration, and the formation of scar tissue Diffuse effects of the same kind are also produced Scattered minute hemorrhages and edema are common Diffuse destruction of nerve tissue can also occur in parts not directly affected by the injury Head injuries even without demonstrable damage to the skull may produce focal brain lesions Concussion may follow either severe or mild trauma Occasionally, subarachnoid or dural hemorrhage may follow when the patient usually but not invariably lapses into coma Concussion may develop as the result of a direct or indirect blow or even by sudden change in air pressure such as is caused by a violent explosion

According to Palmer (28) the acute traumatic psychosis following major concussion is characterized by a definite sequence in the stages of recovery (1) coma, (2) stupor, (3) semistupor (4) dazed bewilderment, (5) Korsakoff phase (6) residual euphoria and (7) recovery Vaccaro (29) believes psychosis may be presumed if (1) it follows immediately after trauma to the head and is characterized by irritability and hypochrondia, (2) any other preceding or intercurrent cause such as infectious disease, can be excluded, (3) the injury has been limited to the head and is of a serious nature and (4) the psychosis has developed within a period of from three to five years

The post traumatic state is often colored by the expectation of compensation and the apprehension of litigation Whether the injured person is conscious of such an influence it frequently is the dominant motive in the prolongation of the victim s symptoms and complaints To be on his guard the physician should know the following facts and observations (1) the patient s normal personality (2) the patient's past nervous or mental history (3) his domestic state (4) alcoholic history (5) financial status and general reputation (6) his veracity (7) his attitude toward litigation or securing compensation (8) whether he has cooperated in his medical treatment (9) his intellectual level (10) his efforts to exaggerate the symptoms or any attempts at malingering and (11) his susceptibility to suggestion

A retrospective diagnosis of concussion must be based upon details concerning the conduct of the patient at the time of, or immediately following the accident The following facts should be ascertained and recorded (1) Did he walk home himself, or ride home alone in the street car, or drive his own car from the scene? (2) Did he assist others in the same accident? (3) Did he enter into lively, active and possibly angry discussion of the accident? (4) Did he show a clear recollection of the details of the accident?—If so the presumption of shock or concussion is most improbable and the etiological relationship of the injury is correspondingly doubtful

It is possible however for a person to develop a neurosis after injury of purely psychic origin an imaginary complex built up by his constant brooding over an impending lawsuit If, after the accident the injured person displayed no hypochondriacal obsessions and resumed work almost immediately, and only after weeks or months began to manifest neurotic symptoms the condition is probably a compensation hysteria This lapse of a distinct interval after the accident one devoid of symptoms is characteristic of a litigation neurosis

Following an injury the adverse mental influences arising out of the accident combine with the traits of a weak personality and oppose the natural tendency to recovery This departure from the normal trend towards recovery is called the *precipitation point'* by Schaller (30) and averages three months and seventeen days after injury It is curious to find that separate investigators Fay (31) and Munro (32) have reached approximately the same result on separate and independent inquiries of the normal recovery time following head injuries

DIFFERENTIAL DIAGNOSIS POST TRAUMATIC PSYCHONEUROSIS AND CONCUSSION

From a study of 100 selected cases of concussion with severe injury and 100 selected cases of psychoneurosis with slight head injury and no appreciable period of unconsciousness Schaller has compiled a comparison of the

TABLE LX

	Post Traumatic Psychoneurotic State (Psychoneurosis) Hysteria	Post Traumatic Concussion State Traumatic Encephalopathy
1	Does not wish to work	Wishes to work
2	Depressed emotional complaining	Euphoric aggressive period of explosive irritability
3	Mentally alert	Amnesia of injury memory and concentration difficult
4	Aggravation of inherent personality defects	Changes from original personality makeup
5	Frequently slight injury	Often severe injury followed by period of unconsciousness
6	Hysterical symptoms and signs	No hysterical symptoms and signs
7	Exaggeration and elaboration in statement and behavior	No exaggeration or elaboration
8	Course Tendency to aggravation	Course Tendency to improvement
9	Favorable effect of termination of compensation or of settlement	No effect of termination of compensation or of settlement
10	Multiplicity changeability and indefiniteness of symptoms	Constant and precise symptomatology
11	Headache rarely absent	Headache frequently absent
12	Dizziness giddiness	Dizziness vertigo
13	No disturbance of tolerance to heat and alcohol	Intolerance to heat and alcohol

features common to the two conditions which form the basis of a useful differential diagnosis

The post traumatic syndrome is one of the most perplexing problems in medicine and great controversy rages as to the relative importance of a psychogenic and a physiogenic factor in its causation Much can be done to prevent the development of this syndrome by the physician who treats the case immediately after the injury The patient s and the family s fears of insanity should be dispelled and a vacillating overcautious attitude avoided The headaches should be made light of and confident encouragement given at every opportunity The patient must be told firmly that he has sustained no injury to his skull or brain and that the symptoms are merely the outward manifestation of his anxiety One should at all costs avoid suggesting a serious injury when none exists and by all means should not hospitalize him for a minor injury

NEUROPSYCHIATRIC PSYCHOMATIC CASE HISTORY RECORD

Date

Name *Address* *Occupation* *Age* *Race*
S *M* *W* *D* *Sep* Ref

Chief Complaint Headache Vomiting Dizziness Convulsions Pain Paresthesia Paralysis Vision Hearing Speech Swallowing Bladder Rectal Nausea Anxiety Tics Insomnia Cushion or girdle sensation *Numbness* *Other*

Present Illness Calender date onset
Probable cause in opinion of patient Trauma Exposure Overwork Strain Other
Gradual—sudden onset Coma? What doing at time of onset
Duration of attack Medication Results
Narrative

Symptom Review Headaches Location Type Onset date Periodicity
Eyes Vision Diplopia Inflammations Glasses Other
Nose Frequent colds Obstructions Epistaxis Operations
Ears Hearing Earache Tinnitus Otitis media Discharge
Teeth Pain Bleeding gums Receding gums Extractions Dentures
Throat Sore throats Tonsillitis Quinsy Hoarseness Other
Neck Enlarged thyroid Periodicity Before or after puberty established Relation to menses Pregnancy Lactation Strains
Respiratory Pain associated with respiration Onset Course Cough Sputum Hemoptysis Night sweats Fever Asthma Hay fever
Cardiovascular Precordial distress Radiation of pain Type pain Onset circumstances Duration Agents of relief Effect of exercise Effect of eating Drugs Cyanosis Dyspnea Palpitation Orthopnea Edema Known heart disease Treatment Results

Gastrointestinal Appetite Digestion Bowel function Diarrhea Constipation Nausea Vomiting Jaundice Pain constant—a c —p c —relieved by Duration of pain Periodicity Chronicity Radiates

Genitourinary Frequency Duration Dysuria Nocturia Polyuria Oliguria Hematuria Discharge Dribbling Caliber of stream Edema of face Pain—radiation Effect of position Medication Results of medication
Gonorrhea Date Treatment Complications
Syphilis Date Primary Secondaries Tertiary
Treatment record
Blood serology Spinal tap
Menses Onset Dysmenorrhea Menorrhagia Last period Discharge
Extremities Pain Tenderness Atrophy Disability or deformity Other Weakness or paralysis Numbness Tingling

Other Symptoms Bedwetting Fits or convulsions
Lose consciousness? Insomnia
Head or back injury Ever faint? Under what circumstances?

Weak dizzy spells Muscle twitch
Shakes or spasms Marked weight change
Temper outbursts How often? Uncontrollable at times?
Change of mood Gay—depressed at times Snap out of it? How?
Get moody blue often or very easily?
Get discouraged with no regard as to whether you keep going on or not?
Periods when you feel unusually peppy or wanted to do big things?
(If cyclothymic establish extent of instability)
What do you do about insomnia?
Tire more easily than you think you should?
Take tonics—nerve medicines—iron—laxatives—vitamins?
For how long? Record names of drugs taken
Any difficulties that come and go with heart sinus stomach trouble?
Do you feel that you must do things in a certain way?
How do you feel toward life?
Have you ever tried to forget these ideas?
Do you find you cannot get rid of these ideas?
Why not?
These things must have made you very nervous—in what way have they done so?

Are there times when you feel happier?
(Elaborate on the above in detail)

Past History Scarlatina Diphtheria Measles Mumps Sm Pox Ch Pox
Pneumonia Rheumatic fever Influenza Fevers Typhoid Malaria
Rheumatism Tuberculosis Chorea Sore throats Paralysis

Traumatic Surgical
Previous hospitalizations Diagnosis Date
Diagnosis Date
Diagnosis Date
Alcoholic history
Previous government service
Ever had a medical or inaptitude (blue) discharge from any Service?
Receiving any government compensation for disability? For what?
Infancy Normal birth Stillbirths in family? Nervous child Convulsions Bed wetting Teething Walking Endocrine
Childhood Frail Strong Thumb-sucking Nail biting Nightmares Fears Tantrums Unusual attachments Adapt to other children
Adolescence Age entered school Leader or follower at games Truancy
Grammar school 1 2 3 4 5 6 7 8 grade High school 1 2 3 4 College 1 2 3 4
Age left school Ambitious for education Reason for leaving school health
Indifference Expulsion Economic reasons
Education obtained under sacrifice of self Parents Brother Sister Wife
Desired education obtained or is there longing for more?
Caliber of school work
Reaction to adolescence—puberty
Where live as a child Where live now
When did you leave childhood home Why?
Was your childhood happy Home life happy
Well cared for Friends allowed in the home
Were recreations and good times encouraged
Did you have or share any responsibilities in the home
Father's occupation Parents get along together
Did you get along with them Get along with brothers or sisters
Did your parents move around much Miss your childhood home?

Occupational History At present has permanent temporary position unemployed
Encircle number of jobs held 1 2 3 4 5 6 7 8 9 in last 1 2 3 4 5 6 7 8 9 10 years
Longest time on one job week—month—1 2 3 4 5 6 7 8 9 10 15 20 25 30 years
Rough per cent of adult life unemployed (encircle) 5 10 25 35 50 75 90 100% WPA
Type of worker Incompetent Undependable Dependable
Attitude Ambitious Overserious Indifferent Shiftless Enjoy work Lazy Any vocational aims? Satisfied with status quo
Had to support any member of family? When you weren't working who supported you
Get along with boss Fellow workers
Promotions or demotions in last 1 2 3 4 5 6 7 8 9 10 or more years
Are any fellow workers getting promoted faster or are being shown more favor than you?

Social and Sexual Adjustment and Development
What age did sex interest manifest itself? How met by parents
Was sexual information given freely—reluctantly—directly—reading matter
Was there any fear Disgust Shame surrounding the onset of the menses
Any sexual problems or worries?

How is your sex power How satisfied How often
Enjoyed by you? By partner Extramarital relations
Why the need for same—and how often?
Practice withdrawal? Unnatural practices How often
For how long Partner cooperate
Married Widowed Separated Divorced Deserted Remarried Single
Length of courtship Age at marriage Disparity of age of marital partner
If contraceptives used how regarded by both from religious aesthetic standpoint?
Does fear of pregnancy exist
Go to church Benefit by attendance Parental attitude toward religion Religious as adolescent Changed now
Tolerant of religious differences Have religious beliefs caused a conflict in regard to marriage Sex Securing a position

Where did patient meet mate? Occupation of mate
Does he or she work now? Is work away from home city For how long
Is this caused by preference or necessity
How is home arranged
Number of rooms Where do relatives sleep Any conflict with the relatives

Do own house work Arise what time in morning Activities after breakfast
Lunch Dinner
Any outside interests? Shared by mate
Hobbies? Friendships easily made Have friends treated the patient well
Many friends Of opposite sex
Ever felt self conscious in groups Ever felt queer peculiar or different
Planning anything to bring social recognition
Like to go to parties Like to be alone
Have you any enemies working against you or trying to make trouble for you?

Are you nervous? Melancholy Have you ever had a nervous breakdown
Ever had a nervous stomach? Any trouble with your organs?

Family History Who constitutes the family group?

Father Living Dead Cause of death If living—state of health
Mother Living Dead Cause of death If living—state of health
Husband (Age and condition of health)
Wife (Age and condition of health)
Parents Social status Personality traits Severe Tolerant Considerate Ambitious Emotionally stable Unstable Jealous Seclusive Successful Companionable with patient when a child Affectionate
Siblings (Health and outstanding personality traits)

History of (name which relative) Epilepsy Psychosis Alcoholism Nervous breakdown Suicide Invalidism Tuberculosis Goitre Diabetes Arthritis Asthma Hay fever Cerebral hemorrhage Obesity Heart disease Hypertension Kidney disease Cancer Syphilis Congenital deformity

Behavior and Attitude Ever get into jams with the law? Ever get the shakes or the D T s Ever had a serious car accident How many of them? Auto license taken away from you? Any judgments pending against you? Are you bringing suit again t anybody?
(Check if present) Grimace Fidget Frightened Glance behind often Normal Tidy Accessible Careless Disordered Sick Restless Alert Depressed Queer Brooding Agitated Negativistic Stupor Stereotypy

General Motility Normal Compulsive Overactive Diminished
Speech Normal Increased Clangy Diminished Disordered Boastful Guarded Disconnected Explosive Profanity Vulgar Indistinct Slurred Will not talk Staccato Test phrases Hippopotamus Methodist Episcopal Irish Constabulary Pound the rugged rock the ragged rascal ran
Handwriting Describe any abnormality
Can patient strike out letters or numbers from a written or printed sheet?

Emotional State Natural Depressed Anxious Elated Suspicious Euphoric Gay Indifferent Apathetic Inconstancy Perplexed Angry Dull Sullen Irritable Inadequate Changeable Silly Unreality Disgust Childish Optimistic Pleasant Adequate Excited Other

Character of Thinking Process *Clear Logical Relevant Rambling Flight* Slow Compulsive Obsessive Diminished Blocking Other

Trends of Thought—Preoccupations Anxieties Fears Compulsions Obsessions (Wash Count Tics Negativism) Phobias Delusions Persecutions Expansiveness Hypochondriasis Reference Influence Unworthiness Sin Guilt Suicidal Ideas Phantasies Visions Hallucinations Voices Loss of organs Echopraxia Ecolalia Verbigeration Catalepsy

Questions of value to bring out above information—copy answer verbatim!
How do you get along with your family?
With people in general?
Have you any friends?
Do they come and see you?
How do you sleep at night?
What are the noises that are keeping you awake?
Why do people wish to kill you?
Have you ever tried to resist?
Is anything else bothering you?
Do you feel your boss co workers friends or family treat you fairly?

Have you any enemies working against you or trying to make trouble for you?
Why are they trying to do this to you?

Mental Grasp Attention easily held Catatonia
Wander Understand what said? Recognize objects?
Orientation Time Place Hour Day Month Year
Name Parent s name Birthplace
Name of President *Previous president* *Governor*
Problems What time would it be if the hands of the clock were reversed?
What is the value of the coins in my hand? How many coins are there?
100 minus 7 equals Interest on $50 at 6% interest for 1 year is
Count from 20 to 1 backwards as fast as you can
Retention Repeat number forward *31749* reversed *31879* forward *9728145*
Recall the address 150 East 6th Street at the end of 5 minutes
Use the words man boy dog and gun in a sentence
Discuss yesterday s activity—what food eaten?
Judgment Detect absurdities I have three brothers John Frank and myself
Difference between water and ice
Difference between horse and ox
Difference between dwarf and child
Difference between mistake and a lie
Difference between corn and oats
Reasoning What does he think of himself?
Does he consider himself really sick?
Opinion of State of his family
Finances and business
Politics World Affairs

Summary

Dreams (Describe the character)

Estimated Intellectual Level and Mental Makeup Superior High Average Average Low Borderline Subnormal Open Depressed Cyclothymic Shut in Paranoid Emotional Inadequate Deteriorated Eccentric Psychoneurotic Psychopathic Defective

Physical Examination Temperature Pulse Respiration Blood Pressure
Habitus Height Weight Development Gait Station
Deformity Tremors Tics Athetosis
Head Pupils react E O M I O T Sclerae Conjunctivae
Exophthalmos Enophthalmos Vision O D O S Fundus
Skull *Hair distribution* Facial symmetry Ears
Nose Mouth Mucosa Teeth Tongue
Throat Tonsils Pharynx Uvula Gag reflex

Neck Thyroid Adenopathy Pulsations Restricted motion
Thorax Habitus Symmetrical Deformity Respiration type
Rise of diaphragm Retractions equal expansion
Lungs Palpation lag
Percussion Clavicular fossae
Auscultation Amphoric quality
Breasts Masses Nodules
Heart Precordial thrust Maximal apical impulse in interspace cm to left of line
Enlargement Thrills Murmurs A_2 P_2
Extrasystoles Heart sounds
Pulse Venous engorgement of neck vessels Edema of
Abdomen Type Size Visible peristalsis Rigidity Masses
Hernia Tenderness Liver Kidney Spleen G Bladder
Other
Rectal Hemorrhoids Prostate *Genitalia*
Reflexes *Skin* Color Pigmentation Jaundice Dry

Summary and Diagnostic Impression

KENT EMERGENCY TEST

This test consists of three overlapping scales with independent norms

Lower scale groups 1 2 3
Middle scale groups 1 3 4
Upper scale groups 1 4 5

General Instructions

In presenting the test always begin with the first group which is common to all three scales For a subject of high grade mentality proceed next to group 4 so as to leave the final choice between the upper and middle scales but for a subject of apparently low grade mentality as indicated by the initial responses group 3 should be given next after group 1 thus leaving the choice open between the middle and lower scales

For a middle grade subject it is permissible to use four groups of questions so as to obtain two ratings but it is not desirable except at the ten year level to use all three scales for any given subject Group 2 should never be used for a subject of high grade ability nor group 5 for a low grade

The test is not intended for a rigidly mechanical presentation but is rather to be adapted to the individual subject The examination should be made as comfortable and inoffensive as possible The examiner may take liberties with the order of presentation especially within a group of questions It is important to bring the examination to a close with a question which the subject can answer correctly and with confidence In order to avoid two consecutive failures it is well for the examiner to have at hand a supplementary list of easy questions which can be introduced as part of the test

As this is not a test of comprehension the subject is entitled to whatever help he may require to understand the meaning of any questions The examiner may feel free to state the questions in his own words using a conversational tone The diction may be adapted to the comprehension of the subject

In order to encourage a timid child to respond it may be necessary to praise every correct answer—his occasional inquiry on any point should be answered truthfully if it cannot be evaded In general the best way to restore a subject s confidence after a frank failure is to pass on quickly to a question which he can answer correctly

Occasionally but not too frequently the examiner may take liberties with the scoring A response distinctly superior to any response mentioned in the key may be allowed an additional point credit or a point may be deducted when the response is clearly inferior to the response in the key which it most closely resembles Responses not covered by the key should be recorded in full and evaluated at leisure

Group 1

	Value
1 *What are houses made of? Any materials you can think of*	1–4
One point for each item up to four	
2 *What is money made of?*	1–5
Gold silver copper nickel paper one point each	
3 *Why does a cork float on water?*	1–3
Explain float if necessary One point for light lighter not so heavy Two points for lighter than water Three points for lighter than the water it displaces No credit for full of air	

4 *What is sand used for?* 1 2 4
Four points for manufacture of glass Two points for mixing with concrete road building or any other constructive use One point for crubbing or play Credits are not cumulative
5 *If the flag floats to the south from what direction is the wind blowing?* 3
Three points for north No partial credits It is permissable to say Which way is the wind coming from?

Group 2

(for young children only)

6 *Where do fishes live?* 1
Water or any body of water, one point
7 *What is candy made of?* 1–2
Two points for sugar with no additional credit for other items One point each for minor materials up to two
8 *What color is the color of grass?* 1–2
One point for green Additional point when brown or yellow is mentioned in addition to green
9 *How many days in the week?* 1–2
Two points when the answer is given easily without hesitation One point for naming the days and counting correctly
10 *What does ice become when it melts?* 1
Water one point

Group 3

11 *How many minutes in an hour?* 1
Sixty one point
12 *How many days in a month?* 1–3
Thirty and thirty-one one point each and one additional point for twenty-eight or twenty nine referring pecifically to February but no credit for twenty-eight referring to 4 weeks
13 *Why is it colder at night than in the day time?* 1–3
Two points for Sun goes down or any response indicating recognition of direct rays of sun as a source of heat One additional point for including rotation of the earth in the explanation If the child cannot answer the question may be reversed What makes it warmer in the day time than at night? Only one point for correct answer to reversed question
14 *Tell me the names of some birds* 1–4
One point each up to four When the subject stops encourage him to continue
15 *Now the names of some fishes* 1–4
One point each up to four

Group 4

16 *What time of day is your shadow shortest?* 3
Noon three points
17 *Give the names of some large cities* 1–4
One point each up to four No credits for home town unless it is an outstanding city If any state be named as a city New York is counted as a state unless given specifically as New York City
18 *What is paper made of?* 1–3
Wood or pulp rags cornstalks one point each
19 *How many stripes in the flag?* 2
Thirteen two points A subject who respond forty-eight should have his attention called to the mistake and should be permitted to correct it When a ubject respond seven explain that the question refers to both red and white stripes
20 *Whose picture is on a two-cent stamp* 2–3
Washington two points One additional point for additional mention of pecial issue but no credit when Washington is omitted

Group 5

21 *What is the difference between a cable and a chain?* 1–4
Explain cable if necessary by use (Elevators guy wires) Four points for clear distinction between continuous strand and detached links One point for chain had links Two or three points for intermediate response referring to structural difference No credit for distinction in use of material

22 *Why does the moon look larger than the stars?* 2-4
Make it clear that the stars are referred to individually rather than collectively and give assurance that the moon is actually smaller than any star Two points for 'Moon is lower down Three points for nearer or closer Four points for generalized statement that the nearer object looks larger than the distant object

23 *Which metal is attracted by a magnet?* 2-4
Four points for iron two for steel

24 *What is electricity used for?* 1-4
Light heat power one point each Only one point for several things run by motors or for more than one specific use of heat One additional point for specialized uses such as telephone x ray radio etc Full credit for statement that power covers all uses

25 *If your shadow points to the northeast where is the sun?* 5
Four points for southwest no partial credits

TENTATIVE NORMS

Table of norm based on 500 subjects The preferred scale for any subject is the one which brings his rating nearest to the middle of the scale The end levels are less trustworthy

Age	Lower Scale Points	Middle Scale Points	Upper Scale Points	Age
5	5-8			
6	9-12			
7	13-17			
8	18-22	16-20		
9	23-27	21-26	17-21	9
10	28-31	27-31	22-26	10
11	32-	32-35	27-31	11
		36-38	32-35	12
		39-41	36-40	13
		42-46	41-45	14
		47-	46-	14 plus

Reference Kent G H *Mental Measurement Monograph* #9 *January* 1932

FINDINGS IN THE HISTORY AND EXAMINATION OF ANY PATIENT SUGGESTING NERVOUS OR MENTAL DISEASES

There is little reason why the average physician as well as the psychiatrist cannot also detect deviations from the normal A careful history from the patient or his relatives a study of his demeanor while he is being interrogated and a thorough physical examination should make it possible for a general practitioner to make a tentative diagnosis of mental disease The case history form on page 957 may be of assistance for those who have no routine or established method of taking a psychiatric history It is an outline of what comprises a complete psychosomatic case study and is not to be used as a questionnaire

Psychiatric Classifications

No attempts at psychiatric classification and diagnosis of a patient into appropriate classes are on a very stable foundation Fortunately, a diagnosis of this nature does not matter in fact it would be better for all concerned if diagnosis, merely for the sake of classification did not exist, because by far the most important point is to understand the disorder, and the patient himself one must know (1) Under what circumstances it arose, (2) How it is related to the patient s normal condition, (3) What light can be thrown upon the problems and (4) What can be done to help towards a favorable outcome

Findings Suggesting Organic Disease of the Central Nervous System

The patients comprising this group constitute from 30 to 40 per cent of those in public and private psychiatric hospitals In order of their numerical importance they are (1) Psychoses associated with arteriosclerosis of the brain (2) Dementia Paralytica (General paresis) (3) Senile Dementia (4) Presenile psychoses (Pick s disease *Alzheimer s disease*), (5) Post traumatic organic psychosis or dementia and (6) Other organic syndromes, namely

a Post-encephalitic Parkinsonism
b Huntington s chorea

c. Korsakoff's psychosis
d Epilepsy and epileptic equivalents
e Malignant hypertension (headache, hallucinations persecutory trends and anxiety may be present)
f Severe pellagra
g Amyotrophic lateral sclerosis
h Multiple sclerosis
i Diffuse gliosis of the brain
j Residuals of bromide lead and gas poisoning

Findings

1 A long record of successful life performance followed by a striking decline and personality change
2 Evidence of impairment of memory retention and judgement
3 Neurological and serological evidence of involvement of the central nervous system
4 Speech and writing disorders
5 Fits palsies contractures and coma
6 Residuals of toxic damage Korsakoff types central neuritis and bromide lead alcohol and gas residuals

Findings Suggesting Toxic-Organogenic Disorders (Toxic Psychoses)

1 Children aged and arteriosclerotic subjects are affected more than adults in the prime of life
2 Failure in understanding clouding of consciousness disorientation fear and hallucinations
3 Somatic findings suggesting failure in support
Common toxins
a) Ethyl alcohol
b) Bromides
c) Chloroform
d) Ether
e) Cocaine
f) Morphine
g) Marihuana
h) Cannabis indica
i) Hyoscine
j) Digitalis
Diseases often responsible
a) Childhood diseases
b) Pneumonia
c) Typhoid fever
d) Epidemic encephalitis
e) Perirectal abscess
f) Rheumatic fever
g) Early endocarditis
h) Puerperal sepsis
i) Perforating duodenal ulcer
j) Pyelitis
k) Cystitis
l) Ostomyelitis
m) Mediastinitis
n) Poliomyelitis
o) Tuberculous meningitis
p) Otitis media
q) Parotitis
r) Hypoglycemic states
s) Hyperglycemic states approaching coma
t) Exophthalmic goitre crises
u) Uremic states
v) Myocardial failure
w) Alkalosis after severe vomiting
x) Acutely developing myxedema
y) Oxygen deprivation from rapid ascent to high altitudes
z) Post traumatic edema of the brain
4 Variants such as alcoholic hallucinosis with a clear sensorium

Findings Suggesting Constitutional Deficiencies Feeble Mindedness

1 Retarded physical and intellectual development such as age of walking and talking school records and Binet test
2 Hereditary feeble mindedness mongolism amaurotic family idiocy Gaucher's disease and other lipoid disturbances cretinism and syphilis
3 Developmental deficiencies meningitis encephalitis, and other diffuse processes of focal diseases

Findings Suggestive of Ingrained Inability to Conform to the Stress and Strain of Society Psychopathic Personalities or Constitutional Psychopathies

1 In these there is an inadequate emotional response but the intellect remains intact They lack a moral response to their environment In some the intellect may be above normal
2 Long history of inability to fit into the social group
3 They cannot sustain interest in any vocation

4 Being optimistic they are led into money-making schemes which fail to materialize They are easily led by suggestion to drink or perversions
5 Early evidence of poor emotional control, temper tantrums as children and behavior difficulty in school due to changes of mood becoming morose, grouchy, self assertive, undependable, indecisive, impulsive, querulous, callous, undisciplined and egotropic
6 Among this group are kleptomaniacs, *pyromaniacs and pathological* liars There may be an accompanying side psychosis, and when such exists the patient is not legally responsible for his acts

Findings Suggestive of Panic Reactions

1 Acute fear and a marked tendency to misinterpretation of his environment
2 Somatic expression, dilated pupils rapid pulse, sweating and restlessness

Findings Suggesting Schizophrenia (Dementia Praecox)

Before discussing the several types of dementia praecox the general findings suggesting disturbances of content and which should lead one to suspect schizophrenia will be enumerated

1) Twist reactions with fancy born incongruities
   a) Shut in seclusive personality with a tendency to live in phantasy
   b) Odd or impulsive behavior increasing pre occupation
   c) Evidence of the loss of the boundaries between self and the outside world running together of day dreams and historical facts
   d) Auditory and visual hallucinations There are feelings of being influenced ideas of reference, phantastic symbolism and ideas of persecution
   e) Persistent *bodily concern* of bizarre quality
   f) Incongruity of affect and content with abrupt shifts to aversion and hate Indifference
   g) Indecision puzzling, scattering and blocking
   h) Motility disturbances such as posturing, mimicking, grimacing increased *muscle tone and resistance* Mutism
2) Systematized delusion formation with formally correct conduct and grasp
   a) Rigid, proud, sensitive suspicious personality
   b) Inability to adapt to reality or to sense the need for correction
   c) Tendency to systematization by false interpretations
   d) Projections in the form of jealousy, persecution interpretations, and the urge for vindication
   e) Appearance of dominant notions— It has all become clear to me"
   f) Retrospective falsification

SCHIZOPHRENIA—DEMENTIA PRAECOX

This group forms 52 per cent of all the psychoses In the United States more beds are occupied in government and private psychiatric hospitals by this group than by any other (25 to 30 per cent of all admissions) Thirty five per cent of cases recover spontaneously A splitting of the personality is seen as the morbid physiology There is a progressive steady change in the personality with a withdrawal of interest from the environment and accompanied by disorders of thought and mood The brain never shows any pathological change

Cause

A single cause of this reaction type is unknown As a rule males are affected more *than females, and the condition* appears to have a greater incidence in urban than in rural communities It is also greater among the foreign born There is no relation to the ductless glands While poisons are not causative, they may bring latent tendencies to the fore Infections may play a similar role Heredity may be a factor Long before the onset of the symptoms of schizophrenia the patient may be seclusive shy shut in and sensitive He is likely to associate only with his elders or parents and shun the companionship of the opposite sex

Types

There are four types (1) Simple, (2) Hebephrenic, (3) Catatonic and (4) Paranoid which may be typical or atypical

Simple Type The onset is marked by an insidious change in personality He may have been very active in his youth but now there is a loss of interest, emotional blunting and indifference to his environment There is no initiative and he may often change his job His employers consider him harmless but lazy He may get the wanderlust and run away from home, usually 'riding the rods', thus he may easily become a vagrant He is indifferent listless and irresponsible While his intellect is seldom damaged his judgement and insight are usually faulty There is poor emotional tone but his memory and orientation are not impaired The picture is one of social maladaptation

Hebephrenic Type This may occur earlier than the other types The onset may be either insidious or subacute The clinical picture is characterized by disintegration and rapid deterioration of the personality There is incoherence of thought with odd mannerisms and silliness impulsive behavior periodic excitability emotional instability without cause and a bizarre nature of illusional trend There are fantastic ideational processes with ideas of reference and influence

Catatonic Type This usually occurs between fifteen and twenty five years of age The onset may be precipitated by some acute emotional experience such as disappointment in a love affair Varying degrees of unresponsiveness may appear the patient may remain for long periods in one posture which he assumes or in which he is passively placed He may be uncommunicative or even stuporous at one time and markedly excited at another There is alternate excitement, depression and stupor The head may droop with the eyes closed The patient is unclean, he may befoul himself and is insensitive to pain Upon recovery these patients recall all the incidents of their illness Impulsive acts are frequent, such as assaulting their companions or supervisors Echolalia and echopraxia are common In the stuporous stage they resist all movement refusing to walk talk or eat They may close the eyes fists and jaws tightly and make no spontaneous movement, but they are responsive to anyone who will start them walking or moving A statuesque posture may be assumed accompanied by a masked fixed, blank expression Grimacing is common

Paranoid Type This type as its name implies resembles paranoia and is characterized by delusions but, as a rule, the patient is able to think clearly

This form usually develops later in life, from about 30 to 45 years of age There is a slow gradual onset with mental deterioration, severance from reality and many changeable delusions which are illogical, multiple and usually fantastic They may be grandiose persecutory or depressed Ideas of reference are common as are those of influence Hallucinations are often in symbolic relation to instinctive demands and are about as well defined as their speech language and thought Their orientation is strikingly good and their intellect remains intact although their insight is poor Associations are disturbed but the memory is usually good Speech may be spontaneous but guarded

There is an *atypical* form in which the paranoid develops paresis or signs of senility of such prominence as to color the clinical picture

Treatment and Prognosis

There is no specific treatment for schizophrenia Since many children and young persons, who tend to be seclusive and are of the 'shut in type later develop this disease, it is well to encourage them to lead a broader social life with less isolation and to discourage unusually strong attachments to their elders and parents After the disease has developed protection from the stress and strain of life is essential if social adaptation is to be secured In severe cases when the behavior is unpredictable institutional care is necessary Patients do recover from psychotic episodes This is more common in catatonics and paranoid types, and is more likely to occur during the first two years of the disease

Insulin and Metrazol Insulin and metrazol have given much hope but it seems that the original enthusiasm for this form of treatment has not been entirely supported In a report from the Elgin Illinois State Hospital concerning the status of 386 schizophrenic patients at least 1 year after the completion of metrazol

or insulin treatment, it is stated that the percentage of mental improvements was less than that claimed for spontaneous remissions Roberts (33) in a recent paper based upon many cases of the Veterans Administration finds against the insulin shock treatment for schizophrenia In certain cases, electric shock therapy has been reported to be successful Many think that this therapy does not stand on a sound scientific basis It has not been established whether it is safer than metrazol therapy If one may judge from the data of several State hospitals it would appear that metrazol shock therapy is of questionable value in the treatment of schizophrenia Other methods that are being used are picrotoxin and mecholyl and asphyxiation in tanks from which oxygen can be withdrawn and replaced by nitrogen

With regard to cure the catatonic has been most benefitted with the paranoid type next simple and hebephrenic types have the lowest recovery rating being almost unaffected by any modern methods of therapy As to improvement the catatonic simple and paranoid types run about even, the hebephrenic form shows the poorest results The younger the person and the earlier the stage of the disease the better will be the prognosis

MANIC DEPRESSIVE PSYCHOSIS

This syndrome is characterized by emotional states which disable the patient by elation or depression with variations in which these states may be expressed in such a way as to almost escape detection The term manic depressive psychosis embraces simple mania and melancholia recurrent mania and melancholia and cyclic insanity characterized by alternating manic and depressive phases with put any quiescent intervals Between 10 and 20 per cent of the patients admitted to government and private psychiatric hospitals fall into this group Many capable members of society are afflicted Women are affected more than men in the ratio of about 180 to 100 The incidence is greater in the cities and among the foreign born Heredity and constitutional make up of patients are prominent factors in the cause of this disorder

Manic Phase

In the milder types of *hypomania*, there may be little else than a self satisfied feeling accompanied by loquaciousness but no boasting and the person is not obnoxious to his fellow workers He may be successful in his work In the *hypomanic state* the following may be noted

1 The patient is often smiling is self assertive and shows great confidence in himself He is the life of the party' and everything is just ' fine and dandy "
2 Laughter and playfulness with much free movement, gesticulation, and boisterousness is common
3 He is talkative, boastful and flighty Attention is easily gained but it shifts to other subjects with the merest chain of connection
4 The patient is witty, shows great psychomotor activity promotes schemes which usually fall through, and is resentful of distrust that may be shown by others He finally becomes obnoxious in gatherings
5 The attention is as easily distracted as it is gained and the patient lacks insight
6 He is so sure of his ability he may plunge recklessly into some business venture and lose everything Finally the family may seek aid or bring the patient to the physician

Acute Mania This may be characterized by the following findings

1 There is an expansive emotional state with wild excitement exaltation and a tendency to violence
2 There is fluctuation of mood from great euphoria to great anger and excitement Bickering argumentativeness and defensiveness occur frequently Grandiose ideas are common as are exaggerated claims of power and ability Occasionally the periods of elation are punctuated with short periods of sober meditation and sadness
3 Profanity is not uncommon even in women who may expose themselves and invite sexual intercourse
4 There are delusional trends wherein the patient may decorate himself with rags buttons, feathers medals and uniforms

5 Ideas are flighty and there is usually a clang association between the words which sound all right in themselves but have no connection to each other or the general context of his speech
6 Memory is good although it is difficult to test
7 Orientation is usually intact
8 There is little impairment in intellect but the insight is not well preserved
9 There may be loss of weight The patient may sleep but very little although he does not seem to notice it nor complain about it
10 He may be noisy and shout and hurt himself in which case he pays no attention to it
11 He may mistake strangers for relatives and friends and embrace them as such
12 While the patient may appear to be busy all the time he rarely completes any task he sets out to do

Depressive Phase

Mild

1 There is a mild slowing up in activity, the patient may just complain of feeling out of sorts He may have vague complaints such as poor appetite and vague pains and may talk more about such complaints than was his custom before the onset of the illness He may institute vigorous searches for the cause of his supposed disability
2 He may feel sad and physically inadequate to perform his duties or even mingle with people He finds it very difficult to think about anything except a very limited number of topics most of which are very unhappy themes

Severe

1 In severe disorders moaning and groaning are frequent and causes one to wonder whether the patient has pain
2 There is less weeping than one would suppose though in some tears flow on the least provocation Patients are usually worse in the morning hours
3 The thought and mood content is illustrated by such utterances as *everything is lost I am forsaken by the Lord I am no good any more* ' '*Something terrible is about to happen I have committed the unpardonable sin,*" *I am unworthy to live any longer,*' '*My lungs and stomach are rolling away* ' and '*I wish I were dead as I do not deserve to live* "
4 Every motion is an effort, there is marked asthenia, the patient is too tired to walk or get around and only does so if forced to it
5 There is an awesome sense of foreboding that something terrible is about to happen In 30 per cent of patients there are hallucinations such as hearing a voice say so and so is dead because of what you have done or ' you have cancer "
6 The thought processes are greatly retarded but memory and orientation is intact
7 There is an overwhelming sense of inferiority and guilt
8 They may refuse to respond to questions or to take nourishment
9 Stupor may be present The patient has a fixed pre-occupied expression He will not talk and has no interest in his environment He may soil himself Tube feeding may become necessary
10 It must always be kept in mind that depressed or elated patients may commit suicide and for this reason constant vigilance should be practised without the patient being aware of it For this reason hospital or sanatorium care is to be preferred

Treatment and Prognosis

The incidence of manic attacks is usually every six months of depressive attacks every nine or ten months Recurrence does not necessarily follow but is common in those having attacks early in life Depressive states are more frequent in adults Even after several episodes the intelligence may not be affected In a Report of the Commission on New York State Hospital Problems November 30 1942 while no details about electric shock therapy were mentioned the general statement appears that it has been 'especially efficacious in the treatment of manic depressive psychoses and involutional disorders This

is in agreement with the Pennsylvania Hospital which reports that there were 279 cases treated with recovery rates as follows during the period of May 1940 to May 1942

Manic depressive depressed tates	60 per cent
Manic depressive manic states	56 per cent
Involutional depressions	70 per cent
Improved	21 per cent

Shocks were given every other day with eight as the average number of shocks for each patient *Fractures and dislocations which* were common complications in 1940 have been completely eliminated by the use of curare There seems to be a general agreement that electroshock therapy is the best treatment for involutional melancholia In the manic group, there are frequent relapses

Electroshock Therapy As a rule patients are given three shocks weekly—every other day The electrodes are placed on both sides of the forehead and the shock is produced by an alternating current of from 100 to 150 milliamperes lasting from 0 2 to 0 4 second The patient should have a complete physical examination before treatment as well as a thorough neurological examination urine and blood analyses, lateral roentgen studies of the thoracic spine an electrocardiogram and an electroencephalogram

No breakfast is given to these patients on the morning of the treatment and when possible sedation is eliminated as well The risk of fracture is minimized by giving *Intocostrin* (synthetic curare Squibb and Co) intravenously in a dosage of 0 5 mg per pound of body weight All dentures and bridgework are removed and a soft mouth gag inserted The patient is placed on a hard table with a pillow beneath the shoulders to hyperextend the spine Assistants firmly hold the shoulders elbows and knees Following the application of the shock current the patient becomes unconscious and if a sufficient current has been used, tonic and clonic convulsive movements will ensue lasting *from 5 to 10 seconds* A course of treatment includes 10 convulsive seizures The fracture rate is about 1 per cent Death occurs in about 1 patient in 2000 The patient does not remember anything about the treatment and often develops memory defects during its course *These are most disturbing* to some patients and call for reassurance They tend to disappear after several months Since the treatment, in spite of the ease with which it can be given carries with it a definite risk, all patients should be hospitalized while it is being carried out

It must also be pointed out that shock therapy does not supplant the older forms of therapy especially in the milder cases For more information the reader is asked to consult the growing literature on the subject

General Measures are, careful attention to the dietary, which may have to be supplemented with vitamins, regulation of the bowels, induction of sleep by *warm baths*, preceded by sedatives such as, *phenobarbital* grains 1 or 2 The patient should be treated in institutions best *suited for handling such cases and where* occupational therapy and appropriate entertainment can be offered Visiting by relatives should be curtailed as they have difficulty in reconciling the changes in attitude and affection which the patient displays in their presence Bright lights and colors may be over stimulating and when possible the patient should be kept from the stimulating effect of others *Hydrotherapy* in the form of warm or cold wet packs or tepid baths prolonged for several hours are valuable for sedation It will be found that sedative drugs will have to be given in from two to three times the usual dose in order to be effective *Insulin* has no curative effect It is frequently difficult in the mild hypomanic to decide whether hos*pitalization is necessary*

INVOLUTIONAL MELANCHOLIA

There is some debate as to whether this is a separate clinical entity A variety of psychotic phenomena occur at the involution period in both men and women It is one of the critical periods of life for while some lose only their reproductive capacity others lose their social and economic usefulness as well Of the 50 per cent who develop the menopausal syndrome at this period it is believed that about 2 per cent suffer from mental illness The manifestations are depression without retardation anxiety feelings of unreality and hypochondriacal delusions It is seen between the ages of 40 and 55 in women and 50 *and 65 years in men* The ratio in incidence

in men and women is about 5 2 Twenty eight per cent recover spontaneously Suicide is common especially in those men who have been very successful in business and who project their own decline into their busine s and the world at large Their previous good health has made them poorly fitted to tolerate ill health in themselves They are very dejected, moan and groan and complain of the loss of certain organs dizziness tingling, sleeplessness circulatory disturbances and hot flashes

Treatment

As mentioned before *electroshock therapy* is considered by many to be the best treatment Many men have been helped by *testosterone propionate* They must be watched to guard against self destruction

PSYCHOSES DUE TO ALCOHOL

Delirium Tremens

Alcoholic addiction is in reality an intense desire to relieve a state of mind or being or, change one that is less desirable to the state produced by alcohol The problem is hopeless unless the patient resolves to stop the use of alcohol and even then the path will prove stormy

The onset is acute and usually characterized by a great motor restlessness and delirium The pulse rate is increased and the temperature rises Examination reveals a flushed and perspiring face dilated pupils congestion of the conjunctivae tremor of the tongue and fingers indistinct thick speech, and ataxia There may be visual tactile or olfactory hallucinations The visual hallucinations may be terrifying, the patient is afraid to sleep is fearful and apprehensive confu ed and disoriented Consciousness may be clouded In some cases there may be epileptiform seizures

Treatment This is discussed in Diseases of Intoxications page 691 693

Korsakoff s Psychosis (Chronic Alcoholic Delirium)

Tuberculosis diabetes and alcoholism may play a role in the cause of this chronic alcoholic delirium which is characterized by headaches and dizziness falsification of memory disturbed orientation confabulation, aphasia alternation of mood from anxiety to indifference, irritability, and suspicion, syncope, amnesia for events immediate and remote following recovery They are susceptible to external stimulation and suggestions There are usually signs of polyneuritis, such as wrist or foot drop

Acute and Chronic Alcoholic Hallucinosis

In the acute type there are marked visual auditory and olfactory hallucinations which frequently cause the patient great fear He develops delusions of persecution and ideas of reference and may attempt suicide to get away from his would be attackers Orientation and consciousness are normal and clear After recovery there may be total amnesia for the events that happened during the illness In the *chronic type* the psychotic state remains without remissions until deterioration sets in

Chronic Alcoholic Paranoia

Delusions are present and become fixed Deterioration is progressive and the patient becomes abusive, irritable readily angered, careless of his appearance and moody, and sheds tears readily He may be boastful and believe he is great in his particular field of endeavor His ability, whatever it may have been begins to decline and inattention supplants interest He is no longer trustworthy and becomes unreliable and untruthful He is unbearable to his family as delusions of infidelity develop

PSYCHOSES DUE TO MORPHINE

The outstanding features are
- Delusions of persecution and infidelity
- Impairment of concentration power
- Impairment of memory
- Intense jealousy
- Periods of depression with ideas of self destruction

Withdrawal Symptoms These are cramps, diarrhea and pain in the joints

General Considerations

These patients should be treated preferably at narcotic farms or in special and suitably equipped institutions Upon admission, they should be stripped given a hot bath all body

is in agreement with the Pennsylvania Hospital which reports that there were 279 cases treated with recovery rates as follows during the period of May 1940 to May 1942

Manic depressive depressed states	60 per cent
Manic depressive manic states	56 per cent
Involutional depressions	70 per cent
Improved	21 per cent

Shocks were given every other day with eight as the average number of shocks for each patient Fractures and dislocations which were common complications in 1940 have been completely eliminated by the use of curare There seems to be a general agreement that electroshock therapy is the best treatment for involutional melancholia In the manic group there are frequent relapses

Electroshock Therapy As a rule patients are given three shocks weekly—every other day The electrodes are placed on both sides of the forehead and the shock is produced by an alternating current of from 100 to 150 milliamperes lasting from 0 2 to 0 4 second The patient should have a complete physical examination before treatment as well as a thorough *neurological examination* urine and blood analyses lateral roentgen studies of the thoracic spine an electrocardiogram and an electroencephalogram

No breakfast is given to these patients on the morning of the treatment, and when possible sedation is eliminated as well The risk of fracture is minimized by giving *Intocostrin (synthetic curare Squibb and Co)* intravenously in a dosage of 0 5 mg per pound of body weight All dentures and bridgework are removed and a soft mouth gag inserted The patient is placed on a hard table with a pillow beneath the shoulders to hyperextend the spine Assistants firmly hold the shoulders, elbows and knees Following the application of the shock current the patient becomes unconscious and, if a sufficient current has been used tonic and clonic convulsive movements will ensue lasting from 5 to 10 seconds A course of treatment includes 10 convulsive seizures The fracture rate is about 1 per cent Death occurs in about 1 patient in 2000 The patient does not remember anything about the treatment and often develops memory defects during its course These are most disturbing to some patients and call for reassurance They tend to disappear after several months Since the treatment, in spite of the ease with which it can be given, carries with it a definite risk, all patients should be hospitalized while it is being carried out

It must also be pointed out that shock therapy does not supplant the older forms of therapy, especially in the milder cases For more information the reader is asked to consult the growing literature on the subject

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FINDINGS SUGGESTING POOR USE OF ESSENTIALLY NORMAL FUNCTIONS MINOR PSYCHOSES OR PSYCHONEUROSES

1 Excessive prolonged concern over essentially normal bodily functions
2 Anxiety states with fear of impending disaster and bodily expressions such as headaches palpitation, tension, and sweating
3 Obsessive thoughts ritualistic behavior and motor tics which appear to be inescapable even with awareness of their essential usefulness
4 The divorce of essentially normal function and experience from the patient s life through paralysis anesthesias, amnesias dream states and fits, and the inability to restore them

FINDINGS SUGGESTIVE OF NEURESTHENIA OR HYPOCHONDRIA

1 History of some great disappointment in business affecting the patient's economic security, in courtship or an unsuccessful marriage
2 History of sexual incompatibility or some impairment in sexual function
3 Symptoms
   Fatigue
   Depression
   Insomnia
   Night sweats
   Loss of weight and appetite
   Indigestion and bowel irregularity
   Abdominal or chest pain
   Difficulty in concentration
   Loss of ambition
   Pessimism although they profess to be happy
   Irritability
   Lack the inspiration of someone s interest in them
4 These patients may go from doctor to doctor, receiving relief from none They are discouraged with the state of supposed bodily ill health As a rule medicines do not relieve
5 Invalidism is acting as a decoy for the thwarting factor more is expected of the patient than he can do and the symptoms founded upon fear obsession emotional immaturity of false concepts to save him from a breakdown in health The symptoms are protective and defensive in nature and their relief will not cure him

FINDINGS SUGGESTIVE OF ANXIETY HYSTERIA

1 History of an unnatural attachment for others or a dread relationship to others—usually a parent or some other close relative
2 Fear, apprehension and fear of losing the mind, imminent death fainting or being the victim of some horrible disease, of violence to self of violence from others
3 Preoccupations about the sex organs or some impairment in sexual function
4 Moodiness depression and tendency to seclusion
5 Attaches great importance to findings not confirmed by examination such as loss of weight, edema of ankles cyanosis, dyspnea marked asthenia and loss of appetite
6 While a complete examination is necessary it often makes such patients worse since they are now certain that something is wrong with them It is well not to dwell on any part of the examination such as auscultation of the heart or lungs, for the obvious reasons just stated
7 The emotional as well as the physical distress causes the patient to conclude that some serious disease is present
8 He is skeptical and it is hard to keep him on a treatment routine
9 There is an immature personality and a distrust for human beings including the doctor and all assurances of the physician are not only forgotten but disbelieved when an anxiety attack occurs
10 As a rule they will get well only when made to by others
11 They may dictate the treatment and to grant any concessions spells failure for the doctor

PRINCIPLES IN THE TREATMENT OF THE NEUROSES

The principles of psychotherapy are not so difficult that they can not be utilized by those not specializing in psychiatry Psychotherapy is an attempt to change the patient s attitude toward himself, his physical and mental proc

orifices carefully examined and an enema given They should then be given hospital clothes and taken to their room No visitors should be allowed, and no laundry from the outside as the drug can be put into water solution and soaked up in their linen, such as, handkerchiefs or shirt tails It can also be injected with a long fine hypodermic needle into apples and oranges therefore no fruit from the outside should be permitted The patient must sign an agreement to allow his mail to be opened Some are cured by psychotherapy including suggestion of a positive nature Any attention given to these patients is usually well repaid as it makes them feel that they are worth while Strychnine and hot baths have helped restless symptoms If one gives them *nembutal* or *seconal* as a sedative, the nurse should stand by until it has been swallowed since a favorite trick is to pretend to swallow the capsule but to keep it under the tongue until the nurse leaves the room then to spit it out and save it until eight or ten have been collected which are taken at one time

PSYCHOSIS DUE TO COCAINE

As a result of the recent popularity of marijuana, psychosis due to cocaine addiction is now comparatively rare Symptoms before addiction has been fully established are renewed energy a facilitation of the stream of thought euphoria or exhilaration and a sort of reverie or phantasy life which is more pleasing to the addict than his normal self With continued use of the drug there is a distortion of time values and a marked deterioration of moral values There may be delusions of persecution and visual hallucinations The subject becomes argumentative surly irritable, confused and the sensorium may be disturbed Visual hallucinations may be very troublesome and restlessness increase until the patient has what is called the leaps because he appears to jump around Close study of the patient reveals one with a psychopathic personality, there is a history of loss of weight and appetite as well as an increasing asthenia This is borne out by inspection which usually reveals an emaciated anemic patient with atrophy of the leg and hand muscles and in some cases wrist and ankle drop There may be formication under the skin and the patient may reveal twitching of the muscle groups of the face and legs The pupils are dilated and the pulse rate is increased Tremor of the hands and tongue is evident Speech may be slurred and convulsions occur in the course of the condition In those who sniff the drug there will be dryness of the nasal mucous membranes and, in some cases ulceration or even perforation of the septum

MARIJUANA ADDICTION

The use of this drug has increased sharply in the last five years and has found many users among the younger age groups The drug is called muggles," reefers" or 'weed" by those using it It has been used by many swing' musicians both white and colored who have done not a little in popularizing the habit of smoking marijuana cigarettes The author has known personally many of these musicians who grow the drug in their back yards Many of these misguided people believe and firmly assert that they need the drug in their profession They explain that by its use the time relationship of the musical bar becomes lengthened so that they are able to crowd more embellishments into it, or put another way it affords them a longer time to think and create an original interpolation Marijuana grown in the north is much less potent than that grown in South America or Mexico The maximal effect is achieved if one smokes indoors on an empty stomach The symptoms vary with the basic personality of the individual Many who have taken this drug for long periods experience little else than a feeling of walking on air and a disappearance of time relationships In others and in those little used to the drug the following features may be found

- Auditory and visual hallucinations
- Delusions of persecution
- Ideas of reference
- Sexual conflicts through sexual excitation and visual as well as sexual hallucinations in which assaults may be committed
- Flight of ideas euphoria inclination to be talkative and sing
- Agitation depression insomnia tinnitus and dizziness
- Suicidal attempts may be made

Therapeutic Measures in Neuropsychiatric Patients

Contraindications and Complications of Drug Therapy

Emergency Routine Upon admission the patient is placed in bed in a private room and must have complete rest Care should be taken that there are no sharp instruments about or open windows where the patient might commit suicide If this is considered a possibility, an attendant should watch the patient carefully *Sedation* may be necessary for sleep and the average normal dosage may have to be increased Warm drinks and attention to the fluid intake are important *If the patient is a chronic alcoholic and in delirium tremens, it is very important to exclude pneumonia, since this is an especially serious complication* Quiet and tranquility should reign in the patient's room and it is well for visitors to be excluded at the discretion of the attending physician In most cases a full diet may be taken without difficulty It can be fortified with hypodermic *thiamine chloride* with beneficial results

General Treatment This is based upon specific medical symptomatic therapy as indicated and carried out in quiet, peaceful surroundings in isolation or when patients equally ill or less so are being cared for For the more severely ill patients narcosis is continued for several days Sedation is used at the discretion of the physician to control tension insomnia and anxiety The early use of *suggestion, persuasion* and stimulating measures such as *hydrotherapy* is advised The patient must be reeducated to adjust his life to his real assets There is little to be gained and much to be lost by chiding him over his imaginary illness Physicians who lack the patience and the tolerance necessary to treat such patients should turn them over to others better qualified to do so If one is convinced that personality problems are at the bottom of the patient s difficulties it is useless to be indirect or ' lukewarm ' in the approach or to try and hold the patient by giving him what *he* wants or to fall back on the time honored therapies

The present policy of our insurance companies in regard to the psychoneurotic patient is an example either of ignorance or of indifference They either pay the patient disability claims, or they often seek to declare the psychoneurotic a malingerer in order to have his claims stopped or his policy invalidated Aside from building up ill will against the insurance company, chronic invalidism is fostered Nothing is done for the patient It is to be hoped that this may be remedied in the future The Industrial Health Research Board in Great Britain in 1936 concluded that "to pay a man for a psychoneurotic disability without giving him treatment in the way of psychotherapy was to push him along the downward path to complete and lasting invalidism "

There is danger in continuing treatment for a long period along the old traditional lines with drugs local surgical interference and physiotherapy all of which are often unsuitable for an illness which is emotional in origin Such procedures will surely lead to a fixation of the neurosis and result in a chronic invalid To consider illness as real" only when there is tissue damage of some sort is an obsolete point of view

Continued Treatment This should embrace a gradual increase in mental and physical activity by means of occupational therapy, graduated exercises short periods of recreation social diversion, hobbies and work This schedule is best carried out by a single medical officer under whose guidance, psychotherapy, through discussion explanation and reeducation should be instituted

Physiotherapy Measures of Benefit

Hydrotherapy The patient is given a *continuous* bath lying full length in a tub the water being continually changed within the temperature limits of 95° and 98°F It is used for restlessness nervous tension, anxiety states insomnia and for general toxic effects

Sprays and Showers These are given as needle sprays and hose streams for their tonic and stimulating effects

Massage General massage is sometimes good for its general tonic effect It is also valuable in exhaustion and states of fatigue, especially in combination with mild exercise

Symptomatic Measures and Drug Therapy

Sodium Chloride Sodium chloride is given in doses of 2 grams every four hours if there is

esses as well as his environment There must be established a rapport between the patient and the physician if the treatment is to bear fruit Not only must the patient feel the doctor *sympathizes with him, he also* must have a respect for the ability of the physician to help him This respect is surely not aided by a brusque cold indifferent, suspicious and intolerant attitude on the part of the physician, nor is the patient at all convinced that his soul has been laid bare by a breath taking race through a history and physical examination This base line study should be complete deliberate, and all inclusive with laboratory procedures if necessary *In certain cases, procedures such as roentgen studies of the gastrointestinal tract, or skull, or electrocardiograms should be ordered even if they are not necessary* for their psychic effect in impressing upon the patient's mind that he is being thoroughly studied There should be no turning back or reexamining as in most cases this unsettles the patient and causes confusion and mistrust By some simple analogies the patient is then told that he has no physical ailments but that emotional factors can cause physical derangements which manifest themselves in many diverse ways It should be explained to him that these causative factors need treatment, and that he will get well but that it will require his active cooperation He is aided by interviews in bringing out into the open unwholesome attitudes associated with unhappy or irritating events of the past or present Calm, firm persistent intellectual discussion with the patient repeatedly brings these unpleasant memories into the fore ground of his consciousness until he gradually is able to face these experiences without flinching and what is more their repetition soon causes them to lose their sting ' Much harm can be done by rushing the patient at this stage Such action will provoke alienation distrust and a needless wounding of the patient s pride At the end of several interviews the physician may have glimpsed enough of the patient s background that it is often a good idea to call in certain members of his family and without putting him in a bad light or having him ' lose face, ' to frankly explain to them the nature of his illness and instruct them in ways and means of getting along with him When marital, social, financial and occupational factors are troublesome and in some cases insurmountable, the patient should be calmly and dispassionately led to review the *facts and the alternatives and should be al*lowed to work out a compromise in his own way He should be led to formulate a social economic and recreational plan and encouraged to carry it through

*Generally speaking, vague symptoms in*somnia, tension and asthenia should be ignored and there should be no tampering with foci of infection at this stage Malnutrition may require vitamins and revising the patient s dietary which should be simple *If the situa*tion at home is tense with conflicts brewing, the patient may do better in a hospital or sanatorium General weakness or a "run down ' feeling may be allayed by rest in bed for several *weeks during which time the patient's habits* regarding the use of tobacco, coffee and alcohol can be corrected Sedatives should be administered with judgement, for these patients especially psychoneurotics, may become drug *addicts*

Condition	Probable Causes	Suggested Line of Treatment
Anxiety neurosis	Unsatisfactory sexual experience with psychic trauma Social or eco*nomic insecurity* Fear of illegitimate pregnancy	Remove cause if possible New interests and activities must be substituted *Compromise* formation
Conversion *hysteria*	Occurs in immature and *hypersuggestible* persons Advice to obtain something otherwise not obtainable or to escape an intolerable situation Marital troubles or social or economic insecurity	Remove cause or establish *some compromise* formation
Neuroses the a[illegible] Anxiety hysteria	Psychogenic psychosexual causes often unconscious	Frequently difficult A few may be helped by review *of the facts* in a dispassionate manner bringing out into the open all wholesome attitudes and irritating events of the past Such ventilation causes the repetition to bring about less sting when the matters are faced Some may need analysis
Compulsion —Obsession Neurosis	Psychose [illegible] phase	Analysis may be required in these cases

period of restlessness mild confusion followed by delirium disorientation auditory and visual hallucinations of a bizarre nature memory impairment and delusions Many of these cases reported having taken several doses of bromo-seltzer daily for several years The bromides are respiratory depressants and they should not be used in the following cases

1 Suspected or definite increased intracranial pressure
2 Senility
3 Cerebral arteriosclerosis } due to the increased permeability of the blood cerebro-spinal fluid barrier
4 General paresis

Benzedrine Sulfate There are seven indications for the use of this drug chronic exhaustion in depressive states neurasthenia parkinsonism narcolepsy cataplexy behavior problems in children and alcohol addiction The use of the drug in alcoholic states should be limited to institutionalized patients Four contraindications are recognized In patients over 60 years of age in the presence of moderate or severe hypertension in the presence of cardiac disease and in those not under the care or supervision of a physician The dose is 5 to 10 mg in the morning and at noon time for depression or hypotension

Quinine This drug is used in the treatment of the myotonias If there is an idiosyncrasy for the drug there may be noted gastric discomfort, tinnitus, diarrhea skin eruptions and fever

Nicotinic Acid Not infrequently in stuporous or encephalopathic cases where from 1200 to 1800 milligrams are given for several days the administration of such doses of the drug has been accompanied by disagreeable reactions such as headache nausea vomiting substernal oppression and flushing and even mental depression Since there is no harm caused by these reactions the drug should not be discontinued, although the substitution of nicotinic acid amide well diluted with sodium chloride solution may lessen the flushing

Atropine Hyoscine and Stramonium These drugs are frequently used in *Parkinson's disease* to diminish tremor salivation and rigidity Their prolonged use is accompanied by a cumulative effect and there may be dryness of the skin, mouth and throat flushing, dysphagia indistinct vision for near objects rapid respiration and pulse restlessness and garrulity mania and convulsions Death from asphyxia has been reported

Prostigmine This drug is effectively used both as a diagnostic and therapeutic agent in *myasthenia gravis* (See also page 943 for its use in hemiplegia facial paralysis and associated conditions) Reese, Paskind and Sevringhaus have reported a curare like effect with weakness paralysis and respiratory failure if the dose (15 to 30 mg two or three times daily) is continued for too long a period

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excessive perspiration, delirium or shock, and in conjunction with a full diet and fluids

Insulin and Glucose 100 c c of 50 per cent glucose with 50 units of insulin are given intravenously in cases of shock and delirium

Metrazol and Insulin Shock Therapy As has been pointed out earlier in this chapter our ideas on shock therapy need revision Neither remissions nor recoveries have come up to the earlier hopes and in many clinics the therapy is in disrepute The administration of shock doses is dangerous because of possible cardiac collapse pulmonary edema, or a state of coma from which the patient does not recover With *metrazol* (cardiozol) therapy, asphyxiation pneumonia is the most frequent cause of death *Convulsions should never be induced in one with cardiovascular disease and an electrocardiogram first* should be done as a routine When *curare* or *beta erythroidin HCl* is injected *intravenously prior to metrazol therapy the* severity of the convulsion is diminished and the danger of fracture or dislocation greatly reduced These drugs, however may cause serious respiratory and circulatory embarrassment if they are injected too rapidly Prolonged courses with metrazol are unjustified, since improvement, if it is to take place will usually begin after the first few convulsions

Thiamine Chloride This can be given in dosage of 120 mg intravenously for vitamin B_1 deficiency or with insulin and glucose in shock and delirium therapy

Dilantin Sodium The toxic effects of this drug used in the treatment of epilepsy are dizziness, ataxia tremors blurred vision diplopia and slight nausea They can be allayed by decreasing the dose from the optimum of 0 1-0 2 gram per day Other toxic symptoms reported are a heavy feeling in the epigastrium vomiting nervousness headache, hypertrophy of the gums increased libido dermatitis associated with fever eosinophilia and in female patients increased growth of hair on the face, arms and body

Tincture of Belladonna This is used for the relief of local or general tension It is given in a dosage of from 5 to 10 drops three times daily after meals One should watch for overdosage in the dehydrated patient

Barbiturate Compounds These compounds constitute the most effective and probably the least dangerous of all the sedatives and hypnotics used in the treatment of neuropsychiatry

Luminal (phenobarbital) grains $\frac{1}{2}$ to $\frac{1}{4}$ three times daily after meals for tension, mild sedation or hypertension Larger dosage is safe, for anti convulsant purposes

Sodium amytal is given in doses of 0 2 to 0 5 gm at night as a sedative For the mild hypnoidal state the dose is usually 0 3 to 0 6 gm, intravenously It is regarded as the most potent remedy for the relief of agitation and depression, and effects the greatest possible release from the inhibiting mechanisms in the mute schizophrenic or retarded depressed patient Its slow injection in dilute solutions is without danger except in cases of marked hypertension or hypotension generalized arteriosclerosis, gross cardiac or pulmonary disease, alcoholic psychoses general paralysis of the insane marked senility, and, any patient who may have an increase in the permeability of the blood cerebrospinal fluid barrier

Purpura hemorrhagica has been reported following the administration of *sedoramid* granulocytopenia following *alurate*, and polyneuritis following *evipan* narcosis

Paraldehyde This drug ranks high in the treatment of delirium or for the induction of the mild hypnoidal state Dosage is 6 to 12 c c at night as a sedative, 10 to 15 c c (20 c c by rectum) for delirium

Morphine It should be remembered that morphine is a respiratory depressant and therefore should *never* be used when increased intracranial pressure is present or suspected Other contraindications are (1) the alcoholic patient since he tolerates morphine poorly (2) in suspected brain tumors, since increase in the intracranial pressure and as a consequence interference with the functions of the vital centers is the rule and (3) in any condition when the spinal fluid is thought to be under increased pressure such as uremia or encephalitis

Bromide At the Iowa State Psychopathic Hospital in a routine series of 600 admissions of patients with psychotic and non psychotic disorders bromide was found in significant amounts in 10 per cent (34) Four per cent showed a blood bromide level of 150 milligrams per cent the level at which toxic and psychic manifestations usually appear These symptoms and manifestations are a prodromal

CHAPTER XVII

DIAGNOSIS AND TREATMENT OF COMMON SKIN DISORDERS

Introduction

Every busy practitioner sees diseases of the skin daily in his practice but it seems that they appear more often as atypical forms rather than as represented in text book pictures Often this atypical feature disappears when the patient completely disrobes and is carefully inspected from head to sole It is not unlikely that during this examination, which by the way is the only kind of an examination worthy of the name other areas of involvement will be found which have been entirely unknown to the patient or, perhaps in some cases even concealed purposely by the patient The patient s denial of involvement of areas not at the moment open to inspection is more often than not incorrect and therefore misleading Granted that in certain conditions like scabies a long drawn out history and physical examination is not worth the time consumed, the pernicious habit that some dermatologists have of not allowing the patient to tell them anything either before or after the examination regarding contacts or other information that might be of inestimable value has always bewildered the author

Percy Baird (1) comments on this point Examination prior to history taking encourages snapshotism and is apt to lead to undue subordination of the history In the consideration of difficult diagnostic problems a careful history is immensely valuable its assistance is too often lost in a hastily executed survey of the case and in overzealous confidence in the value of pure skin morphology as a sole diagnostic criterion A vast amount of the common cutaneous ailments are either borderline or nondescript in character, and an opinion based purely on inspection has more the quality of guesswork then would be the case if properly reenforced by evidence pertaining to possible gross dietary aberrations alcoholism, excessive nervous wear and tear, foci of infection internal diseases under treatment by another physician, sources of contagion occupation hobbies etc"

To aid the physician and prevent snap shot diagnoses the author has prepared a case study form for skin diseases The various possibilities in each region reviewed are brought to mind and are helpful in arriving at a differential diagnosis The few minutes which it takes to examine the patient properly and record the findings will often prove worth while in the long run It may take hours or days to correlate the data and it is surely no disgrace to be unable to tell the patient in a few minutes what he has

Many general practitioners lack interest in skin conditions, some are disdainful of the dermatologist and some even hold the theory that there are three kinds of skin conditions which (1) Sulfur will cure (2) Sulfur will not cure and (3) No d——m medicine in the world will cure' Yet there are many conditions which can be cured or at least greatly alleviated by the intelligent use of topical remedies and other treatments at our disposal

DERMATOLOGICAL CASE RECORD

Date *Ref* *Occupation* *How Long*

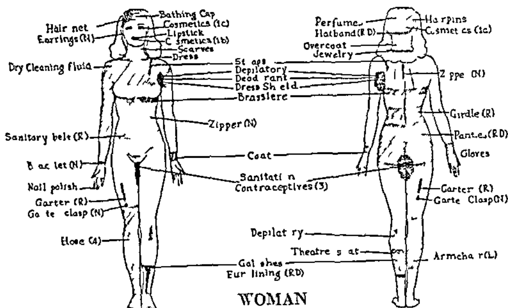
Name *Address* S M W D *Race* *Age*

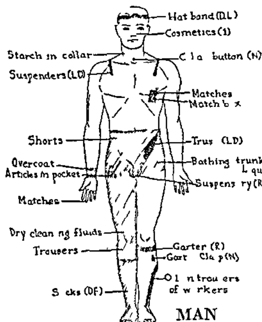
Contacts adhesive arsenic bakelite cade oil carb detergen dust formalin glue goldenrod goat hair iodin iodoform kapoc ipecac inks lead salts laquers leathers dyes mercury salts novocaine nailp ... orris root phosphorus primrose paraphenylene diamin dye picric acid procaine quinine resorcin ragweed resin rayon rubber silk satinwood sulfur timothy tobacco zylonite

Summary of Medical and Surgical Condition

Marital—Sexual Menstrual Pregnancies

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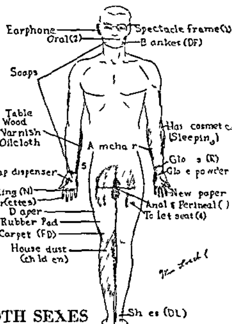


Fig 196 Contact areas (Modified after Dr George L Walbott) (R) Rubber (L) Leather (N) Nickel (F) Fabric (D) Dye

Woman Cosmetics applied to the hair (1a) e g wave setting fluids dyes bleaching fluids perfumes hair tonics pomades cosmetics applied to the face (1b) e g powder perfume creams rouge powder puff cosmetics applied to the eyes (1c) e g mascara eyelash dyes eyela h curler (R) garments sanitary equipment (5) e g chemicals in douches jellies pe aries vaginal suppositories condoms deodorants perfumes sanitary napkins hose (4)

Man Cosmetics (1) either applied e g shaving lotions shaving soap creams or acquired e g lipstick perfume through secondary contact with female articles in trou er pockets e g matches matchbox coins (N) key (N) cigarette lighter (N) fluid in lighter wallet (L)

Both Sexes Spectacle frame (1) also cleansing fluids for lens oral and facial (2) e g chewing gum tooth paste tooth powder mouth wash denture adhesive powder fruit seeds cigarette holders mouthpieces of musical instrument dyes in foodstuffs drugs anal and perineal (3) same as Woman (3) toilet seats (4) e g varnish dyes plastics disinfectants (lysol) fabric of cover watch (5) e g strap leather dyes elastic glass

Present History (Describe)
Duration In other family members?
Previous treatment Effect
Effect
X Ray Treatment Date Dose Result
Date Dose Result
Date last treatment Total dosage Result

Past Skin Diseases (Give dates)
Hay fever Asthma Urticaria Recurrent?
Drugs taken the past 2 months
Cosmetics used the past 2 months
Previous attacks Relation to Food
Season
Environment

Onset Date Acute—Gradual Known or suspected cause
Sites Affected (In order of appearance)
Symptoms Local General
Description of Dermatosis

Areas Involved Head Scalp Forehead Cheek Ears Chin Nose Mouth Lips Eyelids Neck Trunk Shoulders Axillae Chest Abdomen Scapular Interscapular Lumbar Buttocks Perineum Groin Genitalia Extremities Arm Elbow Flexural surface of Extensor surface of Wrist Hand Finger Foot Toes Palm Soles Nails Generalized Universal Partial Hairy surfaces Extensor surfaces Flexural surfaces Exposed surfaces
Type Eruption Macular Papular Pustular Vesicular Bullous Nodular
Arrangement Isolated Discrete Grouped Linear Circinate Coalescing Irregular
Color of Lesions Shape Size
Symmetrical Asymmetrical Acute Subacute Chronic
Examination of Individual Lesions
Macules Color Disappear on pressure Wheal form Infiltration Atrophy
Papules Color Evolution Shape Infiltr Scars Atrophy Stains
Vesicles Tense Flaccid Easily ruptured Contents Serous—Pustular—Hemorrhagic
Scales Color Amount Dry Greasy Loose Firm
Crusts Thin Thick Color Composition
Ulcers Size Depth Edges Floor Secretion Shape Scars

Probable Diagnosis
Scalp Seborrhea Sebaceous cyst Luetic alopecia Alopecia areata Pediculosis
Face Moles Warts Keratoses Rosacea Acne Seborrhea dermatitis
Ears Lupus Seborrhea Staph dermatitis Discharges
Eyes Lues Rosacea Tabes Seborrhea dermatitis
Nose Lupus Syphilis Discharges
Mouth Leucoplakia Mucus patches Vincent s angina Koplick s spots
Axilla Pediculosis pubis Tinea Depilatory dermatitis Furunculosis Folliculitis
Chest and Back Acne Seborrhea Psoriasis Pityriasis rosea Miliaria Folliculitis
Pubic Area Pediculosis pubis Jock strap dermatitis Tinea cruris Erythrasma
Hands Occupational dermatitis Keratoses Tinea Warts Soap dermatitis
Mucous Membranes Leucoplakia Mucous patches

Laboratory Data Wassermann Kahn Kline Darkfield
Urinalysis S G R Sugar Micro
Blood Culture RBC WBC Eos Schilling
Hairs & Scales (KOH)
Biopsy
B M R Blood Sugar NPN

Cutaneous Tests Patch Scratch
Intradermal Tuberculin
Frei Culture

Diagnosis

Recommendations

2 ℞ Na thiosulfate 6 0
Boric acid powder 30 0
Sig Apply to lesion once daily

3 a) 20% Na thiosulfate as a wet dressing 1 hour daily
b) Calamine lotion twice daily

4 Paint with 3% tincture of iodine

5 2% sulfur and alicylic acid ointment for 2 weeks

Tinea Cruris

This condition is very common and is known by such names as *jockey strap itch* and *dhobie itch* It is caused by the Epidermophyton inguinale which is a fungus It is located on the upper and inner surfaces of the thigh but never on the scrotum It has a curved well defined border on its lower edge It may affect both groins but is usually confined largely if not entirely to one side *Treatment* Tincture of iodine diluted 1 4 with alcohol and painted on locally morning and night Other medicaments are one quarter strength Whitfield s ointment applied locally and



Fig 198 Trichophytosis cruris

℞ Bichloride of mercury 0 250
Alcohol 24% q s 210 0
Sig Apply between the toes and in the groins after bath

Erythema Multiforme

Erythema multiforme should not be considered as a clinical entity, it is rather a type of eruption caused by many different causes It is characterized by erythematous nodular, vesicular or bullous lesions, which do not itch and which have a predilection for the dorsal surfaces of the hands and feet as well as the sides of the neck The infection assumes ring like forms and usually disappears within two weeks, although it may last for four weeks The mucous membranes of the lips and fauces are involved and the eruption assumes the form of ruptured bullae with crusting and fetor oris The *general symptoms* consist of fever, itching and some rheumatoid symptoms In severe cases prostration may accompany the eruption Causative factors may be Foci of infection in the tonsils or teeth drugs are commonly thought to be offenders especially bromides iodides salicylates arsenic and phenolphtalein Foods that may be causative factors are, chocolate sea food, pork and nuts Eruptions of the clinical type seen in erythema multiforme are seen sometimes in syphilis leprosy, and streptococcal septicemia It may closely resemble urticaria but this last named affection itches and the individual vesicles last for only a short time Dermatitis herpetiformis is more universal and besides itching violently runs a chronic course

TREATMENT

If the causative factor such as food or drug is known, it should be eliminated Otherwise, the treatment is entirely symptomatic and consists in the application of *talc* or *zinc lotions* In severe bullous cases wet dressings of *aluminum subacetate solution* are of value (one ounce to the pint of water)

ERYTHEMA NODOSUM

The etiology of this disease is not entirely clear It may be due to foci of infection since it often follows inflammatory conditions of the pharynx or tonsils some have found evidence of staphylococcus and streptococcal infections Lomholt and other Scandinavians hold that tuberculosis is one of the commonest causes since they have cultivated tubercle bacilli from the blood the day after the appearance

Intertrigo

Intertrigo is a common condition caused by moisture, warmth, and "kissing" of the parts in areas where the skin is delicate in texture and in a location difficult to keep clean. Other



FIG 197 Intertrigo

causes are, irritation by feces and urine milk in nursing women and lochial or menstrual discharges and diabetes. The *areas involved* are (1) the groins (2) natal cleft (3) infra mammary area in women (4) flexures of the axillae and (5) superior and inner surfaces of the thighs. The affected area is erythematous with maceration of the epidermis. There is often an offensive odor and the secretions may stain but do not stiffen the linen. Most so called cases of intertrigo are believed to be caused by streptococcal or yeast infections.

DIAGNOSIS

Intertrigo should be differentiated from tinea cruris which can be identified by its raised margin and scaling which when examined will reveal the causative fungus. In a very young child or infant congenital syphilis must be excluded. There will be rhagades, snuffles, and bullae on the palms and soles.

TREATMENT

The affected parts should be cleaned with soap and water and dusting powders applied. Cornstarch or soda baths may be of value. A good dusting powder is

℞ Pulv Zinc oxide	16 0
Pulv camphor	6 0
Pulv amyli	32 0

A brassiere or a suspensory may be of help in some cases. In recalcitrant cases fractional doses of x ray are beneficial.

Erythrasma

Erythrasma is chiefly a tropical infection, it is mildly infectious and characterized by slowly developing brown and slightly scaly superficial patches in the groins and axillae and rarely in other intertriginous areas. It *causes slight itching*. *It is differentiated from tinea cruris* by the absence of inflammation and from pityriasis versicolor by the color which is brownish rather than yellowish and by the absence of any tendency to circinate arrangement.

TREATMENT

There are several suggested remedies. One should be cautious in painting iodine on a patient until it is established if there is any sensitivity to the drug as severe burns have resulted.

1 ℞ Alum	3 0
Na hyposulfite	12 0
Boric acid	
Mg carbonate aa	60 0

Sig Apply once daily

Psoriasis

Psoriasis is a chronic recurrent skin eruption characterized by erythematous patches covered with silvery white scales The cause is unknown The sites of predilection are the extensor surfaces of the extremities about the elbows and knees and the calp but the disease may occur anywhere on the body surface it occasionally affects the face The finger nails may be involved with discoloration of the nails pitting and subungual deposits The initial lesion is an unindurated papule covered



Fig 200 Psoriasis

with pearly scales imbricated like the shingles on a roof being thickest in the center of the lesion When the scales are removed pin point bleeding points appear which are the exposed papillae of the corium Papular lesions may coalesce to form plaques The disorder usually clears up spontaneously in the summer only to return in the fall or winter When psoriasis is in an active phase new lesions may be caused by scratches or pin pricks on a normal skin While the general health is not affected an association between arthritis and psoriasis has been observed

TREATMENT

There is an increasing volume of literature suggesting that psoriasis is a disturbance of lipoid metabolism Since 1933, the German medical literature has spoken of cases of psoriasis having been successfully treated by adherence to a diet not exceeding 20 grams of fat daily In 1941 Dragstedt reported that 17 out of 23 patients became free of psoriasis following the ingestion of lipocaic In the early type of lesions Kesten (2) reports excellent results from the use of soy bean phosphatides and defatted wheat germ The soy bean preparation is Lexo cookies (American Lecithin Co) and the dose is from two to five cookies daily The defatted wheat germ is called Vio-Bin (Vio-Bin Corporation) the dose is one to two tablespoons daily

In an acute outbreak of psoriasis soothing lotions should be used When the eruption is chronic the lesions should be stimulated with one of the newer tar preparations 3 per cent *Nu kol tar* (Benet) or 5 per cent *Neo-tar* (Lascoff) ointment or 0 1 to 0 5 per cent *Anthralin* (Abbott) ointment At the beginning the strengths of the ointments should be below average strength they later may be increased if necessary The older vehicles such as lanolin benzoated lard and petrolatum are being replaced with wetting agents in water soluble bases which are non greasy more penetrating and wash off easily They are *Solucreme* (Lascoff) *Hydrosorb base* (Abbott) and *Mull sol* (Hickok) A regime of treatment follows

1 *Internal treatment* is of no benefit except the preparations already mentioned which are worthy of a trial based upon current reports in the literature

2 *Sun bathing* is recommended when possible Ultraviolet light in daily increasing doses is best for those who tan easily—never for acute cases

3 *Roentgen therapy* This may be of value on localized patches (chronic) or on nails not previously treated with x ray It should not be used in children or to check remissions If no results after four treatments of 88 r each the therapy should be discontinued

4 *Foreign Protein Therapy* This should only be used for the chronic types and it

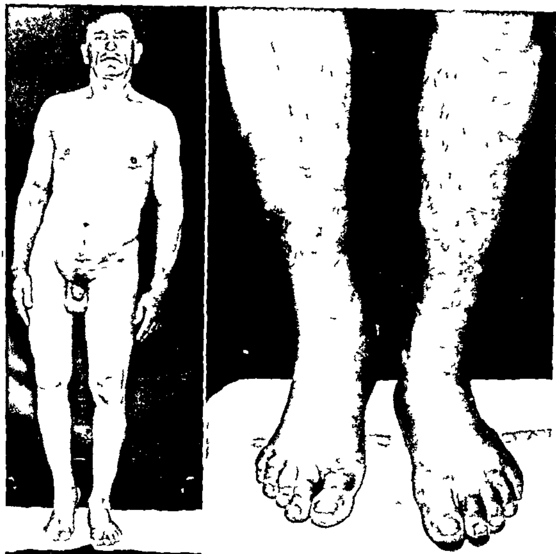


Fig 199 Erythema multiforme

of erythema nodosum They advise putting the patient to bed and examining carefully for tuberculosis elsewhere, with frequent roentgen studies of the lungs When there is doubt, the gastric washings should be examined for tubercle bacilli As a rule the prodromata are more severe than in erythema multiforme There is often high fever and chills The lesions are from 0 5 to 2 0 cm in diameter from pale red to blue in color, tender on pressure and while they fluctuate, they never suppurate They appear in crops on the legs, trunk and face When they disappear in several weeks they leave black and blue marks

The *differential diagnosis* should exclude *drug eruptions* (bromide or iodide), *syphilitic gummas*, and *erythema induratum* which last named is a tuberculous condition seen on the calves of the legs in young females who have a weak peripheral circulation Gumma is unilateral and is usually a single lesion or a small group of distinct lesions Serological microscopical and therapeutic tests are decisive

TREATMENT

The treatment consists of *aspirin sodium salicylate* in ten grain doses every four hours, rest in bed, light diet and the protection of the lesions from the pressure of the bed clothes *Hot boric compresses* may give comfort

Keep coal tar and coal tar pastes in carefully sealed containers to avoid evaporation of volatile ingredients which constitute a valuable part of their efficiency

7 In the scalp 3 per cent *salicylic acid* and 5 to 10 per cent *ammoniated mercury* in petrolatum may be used once or twice weekly with frequent shampooing

Acne Vulgaris

There are probably no skin disorders easier to diagnose than acne but there are few that will require in their treatment more patience and perseverance on the part of both physician and patient Acne is a chronic inflammatory disease of the sebaceous glands and is characterized by the formation of comedones papules and pustules on the face neck and back It is believed to be a physiological activation of the sebaceous system resulting from changes in the endocrine balance coincident with adolescence A very mild acne is almost normal with puberty and while mild to moderate acne can be treated by the general practitioner severe cystic or nodular acne requires the care of a specialist It is poor medicine to dismiss these patients with 'it will disappear in time' An inferiority complex backwardness and timidity in an adult can often be traced to a neglected or untreated acne of years duration It usually takes several months to get rid of the disorder and though the patient should be told that the disease is curable he must be made to understand that he too must co-operate



A Acne vulgaris



B Acneform Eruption

Fig 201

DIFFERENTIAL DIAGNOSIS

Though as a rule the diagnosis can be made without any question one should always exclude *acne rosacea* which occurs at a different age and is mostly confined to the central third of the face Other conditions to exclude are *bromide and iodide eruptions* which will lack the oily background and a *bacterial or mycotic folliculitis* of the bearded region

TREATMENT

This can be divided into local and systemic

The systemic care should include the discontinuance of chocolate iodidized salt white bread and an excess of greasy and sweet foods or any very rich food It is probably *true that*

usually enhances the local treatment Lesions on the body should be covered with 3 per cent *chrysarobin* ointment and those on the face with *ammonium mercury* ointment, *triple typhoid vaccine* is given intravenously, for 5 successive days in gradually increasing doses of 25 to 150 million

5 *Local treatment* of the acute case consists in the use of *calamine lotion* or *zinc oxide starch preparations* If there is pruritus, *phenol* or *liquid carbonis detergens* can be added Oat meal baths are good until the acute inflammatory signs disappear

6 *Management of the Chronic Case* *Chrysarobin* or *crude coal tar* is usually effective If the chrysarobin is proving so one will notice a purplish stain dermatitis of the surrounding parts and blanching of the lesions The following strengths are advised

Acute—none *Subacute*—3 per cent *Chronic*—6 per cent *Inveterate*—10–20 per cent

Patches not responding to chrysarobin will sometimes respond to

Dreue s Ointment

℞ Chrysarobin	12 0
Oil of Cade	12 0
Salicylic acid	6 0
Green soap	*36 0*
Vas alba	100 0

Coal Tar Method of Goeckermann (3)

The improvement following the application of a good coal tar paste followed by ultra violet radiation in ambulatory patients is often as good as that following the use of chrysarobin in hospitalized patients Goeckermann suggests

1 The removal of all scales with green soap and water previous to instituting treatment
2 Application of coal tar paste to the lesions for twenty four hours and then its removal with mineral oil until only a slight brownish stain remains
3 The administration of mercury vapor quartz lamp exposures of just sufficient intensity to avoid a reaction
4 The repetition of this procedure daily increasing the exposures to produce tanning The patient is permitted to take a bath after each exposure before reapplying the ointment

Comments on Coal Tar Therapy Prescribing coal tar and giving the patient adequate instructions is not enough The physician must know the product he is prescribing Not infrequently when one prescribes coal tar the pharmacist will dispense liquor carbonis detergens as a 20 per cent solution in an alcoholic soap bark vehicle Nearly all the coal tars today differ from those originally recommended by such European dermatologists as Brocq Jambon, Dind and others Schamberg was so impressed with the unsatisfactory variability of the coal tars in this country that he imported European tar for his patients Various lots of tar differ and in some cases their use is followed by more harm and irritation than good Two tar preparations are suggested (1) That made under Dr White's suggestions and directions by the Eastern Drug Co Boston Mass, and (2) *Daxalan*, a coal tar paste manufactured by the Dome Chemical Co Inc of New York City The formula for the coal tar is

℞ Crude coal tar	2 88
Zinc oxide	5 37
Starch	53 75
Petrolatum q s ad	100 00

Combes (4) in a recent article mentions some practical points and precautions to observe in the use of coal tar All previous medication should be removed by olive oil or mineral oil The paste is then applied directly with a wooden spatula in a layer just thick enough to cover the lesion Next the area is dusted with talcum until white It is preferable to leave the area uncovered or to use as light a dressing as possible In removing the tar only the loose particles should be removed with mineral oil No attempt should be made to scrub the area The following precautions should be observed

Avoid exposure to direct sunlight of the area to which tar is applied or has recently been applied Tar is a photosensitizer owing to the presence of acridine and anthracene oils

Avoid prolonged use of tar on hairy areas Folliculitis may occur owing to pitch and paraffin oils

Avoid changing the dressing often

Do not apply tar to infected or impetiginous areas

Do not apply tar to more than one quarter of the body surface at one time There is danger of absorption since coal tar contain from 2 to 4 per cent phenol

Be on the lookout for evidence of sensitivity after prolonged use

favor *P ovale* (5) while Stokes, Beerman, Ayres and Anderson (6) (7) favor *D folliculorum*

DIFFERENTIAL DIAGNOSIS

Acne Vulgaris The onset is at puberty, there is characteristic distribution and the presence of comedones and tender infectious pustules are distinctive from rosacea

Lupus Erythematosus There is atrophy and scar formation and no lesions of acneiform type are present

Lupus Vulgaris This is nodular and usually begins in childhood the lesions are soft brownish red and scaly

TREATMENT OF ROSACEA

When the eyes are involved the ophthalmologist should be consulted *Sulfur* is an important part of the therapy and when this is not tolerated *ammoniated mercury* may be substituted *Yellow oxide of mercury boric acid* and *corrosive sublimate* are efficacious for the treatment of the eyelids Baird has outlined a regime under which 80 per cent or more recover

1 Each evening the following ointment should be applied to the forehead cheeks nose chin or affected areas The strength of this ointment which is 10 per cent may not be tolerated by some patients, for these it may be reduced to 5 per cent and for those who require a stronger ointment the strength may be increased to as high as 40 per cent Sulfur can be replaced in the following prescription by ammoniated mercury (5 to 20%)

℞ Sulfur precipitated	3 0
Zinc oxide ung U S P	
Aquaphor (Duke) aa ad	30 0

2 The scalp should be shampooed often the ointment described below should then be applied

℞ Salicylic acid	2 0
Sulfur (ppt)	2 0
Sol coal tar N F	8 0
Aquaphor (Duke)	
Lanolin aa ad	60 0

After the scalp begins to clear the ointment may be applied less frequently and gradually replaced with the following lotion

℞ Mercury bichloride	0 26
Chloral hydrate	24 00
Spirit of formic acid	20 00
Castor oil	4 00
Alcohol (80 per cent) ad	360 00

3 The patient is instructed to keep the hands severely away from the face as it interferes with recovery

4 General treatment includes

a Calcium gluconate in teaspoon doses to half glass of water 30 minutes before each meal and at bedtime

b Dilute hydrochloric acid U S P 20 to 60 drops in fruit juice sucked through a glass tube during meals

c Vitamin D 8000 to 100 000 units daily

5 The diet should be restricted in carbohydrates and alcohol coffee, and tea as well as condiments should be taken in moderation

6 Dilated veins are obliterated by electolysis the needle is put into the dilated vein and allowed to remain until the vein blanches when it is slowly withdrawn with the current on, sealing the opening

7 Telangiectases are sometimes destroyed by freezing with carbon dioxide snow

Pityriasis Rosea

Pityriasis rosea is an acute self limiting skin disorder characterized by superficial scaling patches, round or oval in shape, pinkish to brown in color and for the most part, arranged with their long axes parallel to the cleavage lines of the skin It is most prevalent in the spring and fall of the year The eruption is commonly preceded by what is termed a "mother or herald patch This is a round or oval very slightly indurated reddish plaque which is generally located on the upper trunk or neck It is fawn yellow or pink with a clear center and a fine fringe of scales about the periphery There is no sensation and the lesion is usually not perceptible to the patient From a week to ten days later the generalized eruption appears It extends as a rule from the neck to the midportion of the thighs and is made up of similar but smaller lesions than the

the importance of diet is over emphasized by both the laity and the profession, but it is important that the diet be a well balanced one. Constipation or dysmenorrhea should be corrected. If the basal metabolic rate is low, thyroid medication is advocated by many with good results. In case with a considerable pustular element *quinine bisulfate* is administered 2 to 5 grains three times daily and is said to be of great value in some cases. *Vaccine therapy* is occasionally of benefit. *Ultraviolet light* while conceded to be of symptomatic benefit, should not be considered as curative. *Roentgen therapy*, properly administered is of value but it should be restricted to the older age groups and should never be used to the exclusion of other measures nor should it be used in pustular cases.

Local care includes the vigorous use of soap and warm water applied to the face followed by cold water or an ice rub at least three times daily. Mild toilet soaps are usually astringent enough. Steaming the face and the use of complexion brushes are to be discouraged. Creams should not be used. If the soaps are not astringent enough, tincture of green soap should be prescribed. The patient must be told what the treatment is meant to accomplish. If there is too much drying or chapping of the skin the treatment should be discontinued for a day or two or the lotions made weaker. After washing the face and neck thoroughly with warm water and soap at bedtime, lotio alba is applied.

℞ Zinc sulfate	4 0–15 0
Sulfurated potash	4 0–15 0
Rose water q s ad	120 0

Dissolve each salt in ½ the rose water and mix both together in a mortar stirring constantly.

Sig Apply at bedtime after washing with soap and water.

An equally successful lotion is

℞ Sodium biborate	10 0
Zinc oxide	15 0
Powdered starch	15 0
Lime water	120 0
Rose water q s ad	240 0

Sig Apply this lotion and allow to dry before bedtime. Then apply an ointment containing 2–3% salicylic acid and 3–5% ppt sulfur.

Comedones should be removed by an extractor twice weekly. If this is done more often scarring or hyperpigmentation may be the result. *Sulfathiazole* has been of use when the pustular element is prominent either internally or as an ointment of from 5 per cent to 10 per cent. In selected cases in which no local therapy seems to be of benefit, *roentgen therapy* in a dosage of 75 r each week at 80 to 100 K V for a period of ten weeks offers much benefit.

Acne Rosacea

Acne rosacea is a disease characterized by an inflammatory disturbance of the skin, distributed chiefly over the flush areas of the face, i e the forehead, nose, chin cheeks, and also the scalp. The appearance of the face is characterized by erythema, papules and pustules. In advanced stages the tip and alae of the nose become hypertrophied and in a well developed case presents a red bulbous, rough and nodular rhinophyma. The ages most frequently affected are those between twenty five and thirty five. It is believed to be a form of seborrheic dermatitis due to constant irritation of the skin produced by the deposition on it of the scales and organisms associated with seborrhea. If this factor is appreciated and treated the recovery rate rises strikingly. In fact simple *sulfur ointment* will often be effective after years of dietary regimens, skin tests and elimination diets have accomplished nothing. Overindulgence in alcohol has been said to be one of the causative factors yet the disease occurs in teetotalers. Other factors are said to be gastrointestinal disturbances including constipation achlorhydria and cholecystitis, gynecologic disorders and the menopause during pregnancy or the menses emotional stress high carbohydrate diets and sudden changes in temperature. Some say the disease is prevalent in those who work over hot stoves.

Rosacea is frequently associated with conjunctivitis blepharitis, keratitis and corneal ulcers the last of which may lead to scarring and vascularization of the cornea and impairment of vision. We thus see this disease as one which involves the scalp primarily but capable of invading the eyebrows eyelids conjunctiva and the cornea itself as well as the face and cheeks. It is caused by *Pityrosporum ovale* by *Demodex folliculorum* or some other yeast or fungus organism. Moore, Kile and Engmans

of the penis and the wrist the lesions may assume a ring shaped form The lesions of lichen planus later become confluent to form scaly plaques they are annular gyrate or linear in pattern The lesions of the mucous *membrane may be confused with* leucoplakia If they are limited to the oral mucous membranes they are usually easily diagnosed because of their peculiar morphology which consists of whitish stippling streaks and patches or a lace network effect They may be limited to the vulva The scalp is seldom affected and the face rarely if at all Pigmentation may follow disappearance of the lesion and remain for several months Pruritus may be very severe

Borderline cases may resemble psoriasis but the scales of psoriasis are usually thicker more abundant and leave bleeding points when removed in addition the elbows and knees are usually covered with the scales while in lichen planus the scales are found mainly on the flexor surfaces of the wrists and inner aspects of the thighs and legs Psoriasis is almost never found on the mucous membranes of the mouth When there is any doubt regarding secondary syphilis the blood serologic reaction is usually of diagnostic aid

There is some disagreement about the etiology of the disease There are toxic, neurogenic and microbic theories but at present most writers believe that the cause is neurogenic Jacob and Helmbold (8) have isolated in 25 cases out of 28, a Gram negative anaerobic bacillus from the lesions and were able by inoculation of the organisms into the skin of normal persons to reproduce lesions resembling lichen planus both clinically and histologically This would seem pretty convincing evidence for the theory of infection On the other hand Eller (9) observed acute lichen planus to develop in business men who suffered severe financial losses during the stock market crash

TREATMENT

The best treatment is a double salt of arsenic and mercury called *Enesol* It is a French preparation and is administered intramuscularly in doses of from 1 or 2 c c once or twice weekly for 15 injections It is given in the buttocks *Bismuth subsalicylate* is also valuable given intramuscularly in doses of 1 5 or 2 c c at weekly intervals for from 8 to 12 injections Another drug of which there are good reports is *Bismarsen* It is injected intramuscularly in 0 1 gram doses once weekly for 20 doses Burgess (1) has recently claimed astonishing success with *liver extract* and *thiamine chloride* The liver extract is given twice weekly in 2 c c doses and the thiamine chloride daily in dosage of 3000 international units

Seborrhea Dermatitis

Seborrhea dermatitis is characterized by a persistent oily adherent scaling of the scalp with itching it extends downward to involve the forehead face and ears axillary, inguinal sternal and interscapular areas When of long standing it leads to alopecia At times the lesions become inflamed and there is an exudation of serous fluid and wide extension may follow Characteristic branny scales form upon the skin they are reddish brown in color and greasy The diagnosis is usually easy and should cause no difficulty

TREATMENT

The scalp is the seat of the trouble and should be treated first An ointment containing sulfur should be rubbed well into the scalp and allowed to remain on overnight and the scalp washed the next morning with tincture of green soap On the second night a tonic containing salicylic acid and liquor carbonis detergens is used no treatment is given on the third day The ointment is repeated on the fourth day the shampoo on the fifth and the tonic on the sixth No treatment is given on the 7th day This regime should be repeated and continued faithfully for one month The preparations used in this regime are

Ointment

℞ Oil of cade	6 0
Ppt sulfur	3 0
Salicylic acid	1 5
Ung Aqua rosae	30 0

Shampoo

Tincture of Green soap

Tonic

℞ Salicylic acid	4 0
Liq Carb Detergens	8 0
Camphor water	45 0
Alcohol 95% q s ad	180 0



FIG 202 Pityriasis rosea

mother patch They follow the cleavage lines of the skin It is rare for the face or scalp to be involved and also quite unusual for the lesions to spread distally beyond the elbows or knees Itching may be slight or severe After a few days the lesions begin to peel from the center revealing clear oval lesions with fringes of scales at the periphery The clinical picture remains stationary for about two weeks after which spontaneous involution begins

DIFFERENTIAL DIAGNOSIS

The lack of mucous membrane lesions and adenopathy as well as a negative serologic reaction rules out secondary syphilis The self limiting nature of the disease together with its distribution and arrangement rule out psoriasis and seborrhea dermatitis

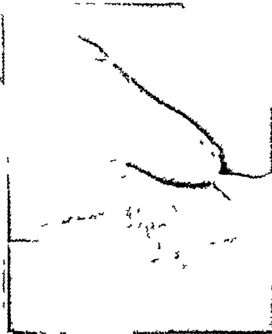
TREATMENT

If the itching is severe *calamine lotion* or *1 or 2 per cent salicylic acid ointment* is valuable Erythema doses biweekly of ultraviolet light cause a rapid involution of the lesions

Lichen Planus

Lichen planus is an inflammatory disease of the skin The *primary* lesion is a shiny flat topped angular papule with a violet color and adherent scales from a pin head to a split pea in size The papules develop in rows along the lines of scratches Some lesions are umbilicated or have a horny plug in the central area Areas of distribution are the flexor surfaces of the wrists the inner aspects of the legs and thighs the penis and the mucous membranes of the mouth and lips Sometimes in the region





B Impetigo contagiosa Note the vesicles and crusting C Herpes zoster with zonal multilocular vesicles

Fig 203 (*continued*)

commonly called cold sores or fever blisters There is a sudden onset with a stinging or burning sensation followed in a few hours by a vesicle upon a reddened base The vesicles dry in about a week running a self limiting course in which the crust that has formed drops off leaving normal skin Recurrences are common in the same area

ETIOLOGY

It is believed that herpes simplex is caused by a filterable virus entering the body through the respiratory passages and localizing about the sensory nerve endings Predisposing factors are indigestion sunburn nervous strain acute febrile diseases and trauma

DIFFERENTIAL DIAGNOSIS

Herpes Progenitalis One should always be wary of syphilis and the least suspicion warrants a dark field examination and repeated Wassermann tests

Impetigo Contagiosa The lesions are pustular the crusts larger and the onset and development is slower

Herpes Zoster The distribution is zonal with multilocular vesicles the lesions are unilateral painful and heal with scarring

TREATMENT

For the first few days *calamine lotion* with or without boric acid compresses are useful In the crusting stage *sulfathiazole ointment* (5%) is used Prevention of recurrences is managed by a series of from two to four fractional roentgen ray exposures of the area involved at 10 day intervals or autoinoculation with the patient s own blister fluid

Dermatitis Herpetiformis

Dermatitis herpetiformis is an eruption of unknown etiology sometimes called Duhring s disease and characterized by the appearance of groups of erythematous vesicles or nodules pustules and bullae associated with itching and burning In pregnant women the disease is called *herpes gestationis* The lesions have a predilection for the extensor surfaces of the elbows the sacral region the trochanteric scapular and knee regions After spontaneous disappearance of the symptoms the lesions are prone to recur Hyperpigmentation accompanies healing Hypersensitivity to bromides and iodides is present in most cases and may aid in the diagnosis Other points which may assist the diagnosis are the herpetiform arrangement of the lesions the absence of lesions

As an alternate routine, the following soap lotions can be followed by the daily use of a hair tonic containing resorcinol

Soap Lotion for Dry Scalp

℞ Soft soap	60 0
Sp vini rect 50%	30 0
Thymol	4 0
Oil of lavender	4 0

Sig Rub in with fingers till lather Then rinse with warm water

Soap Lotion for Greasy Scalp

℞ Ether	8 0
Aq ammonium fort	1 2
Soft soap	60 0

Lotion for Oily Scalp

℞ Mentholis	0 15
Liq Carb Detergens	8 00
Hyd chlor corr	0 12
Alcohol	240 0
Acetone	12 0

Hair Tonic to Follow Above Lotions

℞ Resorcinol	4 0
Balsam Peru	0 1
Olei Myricae	0 6
Olei Ricini	8 0
Alcoholis q s ad	120 0

Cream for Body Areas

5% sulfur and 1% salicylic acid is helpful

Seborrheic Greasy Face Cleaner

℞ Salicylic acid	2 0
Boric acid	4 0
Resorcinol	2 0
Dil alcohol	92 0

Seborrheic Warts

For these softening with 5 per cent salicylic acid for a week or so followed by the application of solid carbon dioxide offers quite uniform results without danger of scarring if the refrigeration is well localized to the lesion itself If this fails electro-coagulation may be used

Herpes Simplex

Herpes simplex is an inflammation of the skin characterized by groups of deep seated vesicles which appear most commonly about the mouth face and genitalia but may appear anywhere on the surface of the skin They are



A. Herpes simplex
Fig 203

on the mucous membranes a benign course and itching and burning as well as capriciousness of the eruption

TREATMENT

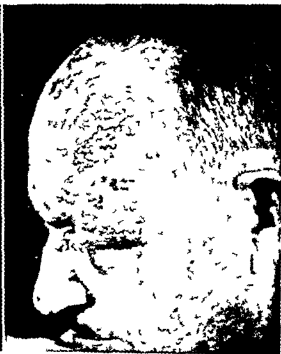
Quinine sulfate 0 2 gram two or three times daily or *Fowler s solution* 10 to 15 drops three times daily are said to be of value The itching may be relieved by adding 2 grams of potassium permanganate to the bath or by the local application of lotions containing phenol or liquid tar

Herpes Zoster

Herpes zoster is an acute inflammatory skin disease characterized by vesicles or papules distributed along the course of some superficial sensory nerve Evidence seems to point to it being essentially an *acute posterior poliomyelitis* due to the virus of chicken pox It is unrelated to herpes simplex Inflammation pressure toxins and hemorrhage stimulate the posterior root ganglia causing an effect equivalent to that caused by stimulating the peripheral ends of the cut posterior nerve roots Dilatation of the blood vessel in patches along the distribution of the involved sensory nerves results Antidromic impulses release H substance (which resembles histamine in its properties) at the nerve endings This substance increases the permeability of the capillary wall causes capillary dilatation and through an axon reflex dilatation of the arteries Thus are caused an exudation of serum and the formation of vesicles along the posterior nerve root distribution of their cutaneous sensory branches If the brachial or lumbosacral plexuses are involved the distribution may not be limited to the course of one peripheral nerve If the gasserian ganglion is affected lesions may be seen on the cornea nose mouth in the auditory canal and skin areas supplied by the fifth cranial nerve The disease is unilateral with very few exceptions There may be severe pain which precedes, accompanies or follows, the herpetic lesions and sometimes persists for years as a post herpetic neuralgia The pain is caused by inflammation of the sensory nerve fibers entering the involved dorsal root ganglions The disease attacks all



A Herpes zoster



B Herpes zoster ophthalmicus

Fig 205



FIG 204 De matitis herpetiformis

Herpes zoster of the ear is treated by the local application of 5 per cent phenol in glycerin or from 1 to 2 per cent salicylic acid in alcohol

Pyogenic Infections of the Skin

The causative organisms of pyogenic infections of the skin are the staphylococci and the streptococci which enter through the orifices of the hair follicles the sweat glands or abrasions Infection may be secondary to pruritic eczemas exfoliative dermatitis scabies and pediculosis

IMPETIGO CONTAGIOSA

Impetigo is perhaps one of the commonest skin diseases of children It is caused by streptococci or staphylococci It can be acquired in barber shops and is spread by direct contact or through the use of infected face towels It usually occurs on the face and scalp and rarely on the limbs or body The early lesions are tiny red spots which soon turn into a small papule then a thin walled vesicle which in turn forms yellow stuck on crusts when the vesicle breaks The fresh crusts are yellow but later turn brown and when mixed with blood they may be black in color A denuded red spot is left after removal of the crusts Itching is prominent and very annoying to the patient Clinical variations are a *circinate form* which simulates ringworm and a *bullous type* caused by staphylococcus aureus occurs in infants and which may become serious owing to its rapid spread over the body and the development of constitutional symptoms This form is called *pemphigus neonatorum* As a rule, the regional lymph glands are not affected In impetigo of the scalp the hair may come out in patches some time after the crusts disappear and be mistaken for syphilitic alopecia

Treatment

After sponging the lesions with *peroxide of hydrogen* the crusts are removed with a forceps and the base of the lesions touched with 2 per cent iodine in pure benzol The patient is given either 5 per cent *sulfathiazol ointment, sulfathiazole powder* (20 per cent concentration) in cod liver oil ointment or *Wyeth's alulotion* which is a colloidal kaolin lotion containing ammoniated mercury In the milder types sometimes encountered a 2 to 5 per cent *ammoniated mercury* ointment will usually suffice

IMPETIGO OF BOCKHART

This is a small pin head follicular pustular eruption seen on the extremities and usually secondary to a furuncle or a discharging sinus or wound It is seen in unkempt patients who pay little attention to their general hygiene it is fairly common in children Local treatment such as 5 per cent sulfathiazole ointment or permanganate wet compresses constitute the treatment

ECTHYMA

This is a deep seated form of impetigo characterized by round or oval excoriations covered

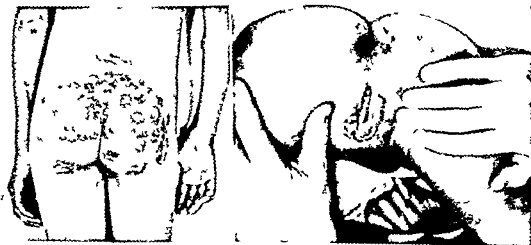


Fig 206 Ecthyma

ages and sexes, and is common in those who are overworked, or ill One attack usually confers immunity although a second attack may occur An attack of zoster may be precipitated through activation of the dormant virus or through a reduction or disturbance of the factors conferring immunity or resistance on the host The commonest "trigger factors" (11) are arsenic, lead, bismuth, mercury, iodides, gold, morphine, carbon dioxide and monoxide, leucemias, trauma, infectious disease such as influenza, encephalitis, erysipelas tuberculosis, and early cardio vascular syphilis, paresis and tabes, vaccination, malignant tumors and Hodgkin's disease

DIAGNOSIS

The diagnosis is usually made from the appearance of the characteristic vesicles or papulo vesicles distributed along the course of a cutaneous nerve and accompanied by pain and tenderness In cases without cutaneous manifestations the *diagnosis may be aided by a lumbar puncture* which will disclose a lymphocytosis of the spinal fluid The diagnosis may not be clear in early cases when there are no vesicles or pain, but only a unilateral patchy erythema As a rule the vesicles appear suddenly The pain may simulate pleurisy kidney stone or gall bladder colic, appendicitis, neuritis or myositis Rarely the disease is bilateral *It is not fatal, contrary to the belief of laymen*

TREATMENT

It is important to keep the lesions dry in order to prevent any re infection, for the virus of zoster is present in the vesicular fluid *Calamine lotion with phenol* is a useful dressing and vesicles so treated will rarely leave scars Other protective dressings used with good results are

1 Flexible collodion
2 Melted paraffin
3 Thick cotton pads
4 10% naftalan
5 2% ichthyol in Lassar s paste
6 Protective lotion

℞ Phenol	2 40
Glycerin	8 00
Na biborate	10 00
Zn oxide	15 00
Powdered starch	15 00
Lime water	120 00
Rose water q s ad	240 00

Ophthalmic zoster is frequently associated with swelling of the eyelids, inflammation and vesiculation of the cornea itself The eye should receive *boric acid* compresses and *irrigations* followed with either 5 per cent *argyrol* or a 1 3000 *bichloride of mercury* ointment Between treatment, it should be protected from the light with a patch In the resistant type of *ophthalmic zoster, diphtheria antitoxin*, 5000 units repeated in two days, has been recommended

Pain in Herpes Zoster

There are many agents at our disposal for the relief of pain Among these are salicylates codeine, phenacetin, and morphine in very severe cases Other therapeutic measures mentioned in the large literature on herpes zoster are

a) *Cobra venom injections* (12) (13) (14) Relief is usually prompt but it is best for psychic reasons not to divulge the nature of the medication
b) *Ethyl chloride spray* This is applied over the affected dorsal root ganglia
c) *Radiant heat* is beneficial in many instances
d) *Filtered roentgen rays* over the dorsal root ganglia both relieves the pain and shortens the course of the disease (15) (16) (17) 148 r are given through a 3 mm *Al filter at a distance of 30 cm*
e) *Intravenous sodium iodide*, 2 grams in 10 c c of water on the first third fifth and seventh day diminishes the pain and hastens the involution process (15) (18) (19)
f) *Subcutaneous injections of pituitrin* 0 5 to 1 0 c c are advised by many, but Goodman and Gilman claim that the mechanism of its action is obscure and evidence of its value contradictory
g) *Thiamin chloride* Herpes zoster occurs quite frequently as a result of large doses of thiamine chloride This suggests that this vitamin has a selective action on the dorsal root ganglia Other cases on adjusted dosage have had a complete amelioration of pain One is referred to the papers of Gordon (20) Rattner and Roll (21) and Smith (22) in which an extensive review of the literature on the use of thiamine hydrochloride is covered

ard forms of treatment There is no prophylactic treatment for warts They are treated as they appear

Verruca Vulgaris

These common warts of the skin may appear on the hands, penis scalp eyelids tongue and almost any other place on the skin

Flat Warts of Childhood

There are generally multiple often numerous and are distributed on the face neck hands wrists and knees

Plantar Warts

These occur on the pressure points of the ball of the foot They are usually contracted by walking barefoot over areas trod by people who carry the disease

Treatment of Warts Bloch (23) who advocated treating warts by suggestion cured 88 per cent of juvenile warts and 44 per cent of



Fig 209 Plantar Wart

common warts by such therapy His experiments were carefully controlled and to those who doubt the validity of his work a perusal of his original paper in German will be most convincing Common warts are easily removed by the application of solid carbon dioxide after a preliminary softening up process with 5 per cent salicylic acid or electrodesiccation under novocain anesthesia Recurrences may occur but are rare after a second treatment In the treatment of flat warts local applications of *ammoniated mercury salicylic acid sulfur* and *resorcin* are often efficacious *Bismuth salicylate* intramuscular therapy is used with good results Baird (24) mentions as an effective therapy the touching of each visible wart lightly with a desiccating needle repeating the procedure once weekly and following each treatment with a small dose of x ray (35 to 75 r) to the affected area—not to each wart For those patients who refuse treatment by x ray surgical excision or diathermy *trichloroacetic acid* may be applied locally The degree of destruction is difficult to control and keloidal scars may result

If technically feasible roentgen therapy is *the best treatment for plantar warts* It is usually employed in a dosage of 300 to 1500 r Before treatment the warts are shaved down, all excess callus removed and the area of normal skin shielded with leaded rubber If the wart fails to respond a second dose may be given but *when two treatments have not sufficed* it is better to forego any further irradiation and to use trichloracetic acid locally Radiation or radium treatment should never be given when there is a previous history of either having been given and to be on the safe side *it is well never to employ irradiation until an accurate record of previous therapy has been made*

Molluscum Contagiosum

This is an autoinoculable disease of the skin which is mildly contagious and characterized by waxy lesions usually presenting a central depression and ranging in size from a pin head to a pea The lesions are discrete as a rule but they may be found in groups As they increase in size they become hemispherical and *attached to the skin by the entire width of the base* At the crest or height of the lesion umbilication is noted and molluscum bodies

with a thick solid crust and surrounded by an inflammatory areola There are usually superficial ulcerations under the crust As it is a deeper lesion than impetigo, it usually leaves scars The lesions occur principally on the lower extremities where the circulation is sluggish The treatment is similar to impetigo *Sulfathiazole* by mouth is said to be rapidly curative *Ultraviolet or roentgen therapy* will limit the spread of the disorder

SYCOSIS VULGARIS

This is a chronic staphylococcal infection of the hair follicles of the bearded area in males



Fig 207 Sycosis vulgaris

It is characterized by pustules and papules pierced by hair which becomes loose and later such areas may become hairless due to destruction of the follicles Scarring and atrophy may follow long standing cases Sycosis on the upper lip may result from a chronic rhinitis The staphylococcus pyogenes aureus is the exciting causative factor Lesions of tinea barbae are differentiated by their being superficial and scaly discoid patches, or deep boggy swellings and by the fact that the trichophyton can be demonstrated

Treatment

This condition is sometimes very resistant to therapy Usual methods include manual epilation, local disinfection with hot dilute *bichloride of mercury solution* (1 5000) and the application at night of *Quinolor ointment (Squibb)* In acute cases 5 per cent *sulfathiazole ointment* in a vanishing cream base should be tried *Roentgen therapy* is useful in some cases

TINEA BARBAE OR BARBER'S ITCH

The diagnosis is usually easily made since the fungus is found on the hairs which can be



Fig 208 Tinea barbae

easily extracted from the diseased follicles The treatment consists of epilation after the application of hot *potassium permanganate* dressings 1 4000 Pustules should be opened *Ammoniated mercury ointment* 10 per cent or with equal portions of boric acid ointment are used locally *Roentgen irradiation* in the hands of the experienced is valuable

VERRUCAE

Warts are considered to be caused by a virus and with few exceptions respond to the stand-



FIG 211 Multiple Neurofibromatosis



FIG 212. Multiple Lipomatosis



A Recklinghausen s disease



B Note the Cafe au lait spots and arrangement along the lines of cleavage

FIG 213



A *Molluscum contagiosum*



B *Umbilicated Lesion of Molluscum contagiosum*

Fig 210

are found in the cheesy material that may be expressed through this central opening

This disease is caused by a filtrable virus and occurs more frequently in children Treatment consists of curettement of the individual lesions, after electrodesiccation

Fibromas

A fibroma of the skin is a benign new growth of fibrous connective tissue cells and fibers They *develop in the cutaneous and subcutaneous* tissue and may be classified as soft (fibroma molle) or hard (fibroma durum), as well as flat, sessile or pedunculated The etiology is as yet unknown although trauma heredity and endocrine factors have been mentioned as possible influences in the causation of such tumors

The hard *fibroma is usually located on the* trunk or the genital region It varies in size from a small pea to a walnut and may have a broad base or it may be pedunculated The soft fibromas may attain the size of a coconut They are frequently seen about the neck face, trunk female genitalia and armpits The treatment of choice *for solitary fibromas* is surgical excision

A generalized type of fibromata is seen in *Recklinghausen s disease* wherein most or all of the tumors are neurofibromata This disease *is seen in both sexes and is characterized* by multiple disseminated tumors of varying sizes color, and consistency which may lie in the skin or project above its surface They may present a broad base or may be pedunculated They have been found on the oral mucosa as well as the mucosa of the bladder, *urethra and colon As the disease progresses*, cafe au lait spots appear resembling the color of coffee with cream The spots are round increase with growth of the patient and they may arrange themselves along the lines of skin cleavage In spite of widespread involvement of the nerve trunks there is but little if any *neurological symptoms or signs* Some patients may show mental lethargy imbecility and clumsiness While the disease is benign malignant changes may occur in some of the lesions The treatment is purely symptomatic and for the most part consists of surgical excision or electrocoagulation of the tumors Attempts to bleach the pigmented spots are usually unsuccessful



C Tinea circinata



D Dermophytosis

Fig 214 (*continued*)

amination under the low power lens the presence of any fungi will be disclosed Common fungus infections of the skin are *tinea circinata tinea cruris tinea versicolor tinea imbricata erythrasma* and *dermatophytosis* the so-called athlete s foot

Tinea cruris usually localized in the inguinal area is caused by *Trichophyton rubrum* or *Epidermophyton floccosum* Tinea circinata is caused by a species of *Trichophyton* or of *Microsporum* Erythrasma is caused by *Actinomyces minutissimus* and tinea versicolor by *Microsporon furfur*

TREATMENT OF FUNGUS INFECTIONS

Tinea Cruris or Eczema Marginatum

The following ointments (26) are efficacious but should be only used at night When ointments are not practical the tincture listed below is useful and may be followed by any of the dusting powders mentioned which are also of some prophylactic value

1 ℞ Thymol 1 0
  Salicylic acid 3 0
  Benzoic acid 5 0
  Lanolin
  Petrolatum aa q s ad 100 0

This approximates one half strength Whitfields and should be used with caution

2 Tincture
  ℞ Salicylic acid
  Boric acid aa 5 0
  Thymol 1 0
  Iodine crystals 1 0
  Alcohol 50% q s ad 100 0

  Sig Paint on twice daily and cover with dusting powder

3 Milder tincture
  ℞ Sodium propionate 10 0
  Salicylic acid 3 0
  Menthol
  Phenol aa 1 0
  Alcohol q s ad 100 0

4 For drying effect (or monilia infection)
  ℞ Gentian violet 0 3-0 6
  Distilled water or alcohol q s ad 30 0

5 Fungistatic dusting powder
  ℞ Salicylic acid
  Zinc stearate
  Boric acid aa 5 0
  Powdered talc 75 0
  Starch q s ad 100 0

6 A stronger dusting powder
  ℞ Sodium pentachlor phenate 0 1
  Benzoic acid 5 0
  Zinc peroxide 30 0
  Boric acid 5 0
  Talc 50 0
  Kieselguhr q s ad 100 0

Fungus Infections

It has been estimated that from 60 to 90 per cent of the population of the United States are or have been affected, at one time or another with a fungus infection Superficial fungus infections are found affecting the glabrous skin the hair and hairy areas and the nails Allergic secondary lesions are called dermatophytids and must be differentiated from the actual fungus infections

CLASSIFICATION

Schwartz (25) has classified the various allergic manifestations to fungi as follows

- I Epidermal trichophytids (epidermis mainly involved)
  - 1 Eczematoid (dyshidrotic)
  - 2 Lichenoid
  - 3 Parakeratotic
  - 4 Psoriasiform
- II Cutaneous dermatophytids (papillary body mostly involved)
  - 1 Diffuse forms
    - a Scarlatiniform exanthemata and enathemata
    - b Erythroderma
  - 2 Circumscribed and disseminated forms
    - a Follicular localizations, usually lichenoid
    - b Not exclusively follicular
      - (1) Macular, papular, and even exudative eruptions
    - c Erysipeloid
- III Subcutaneous dermatophytids (nodules found in the hypoderm of the type of erythema nodosum
  - 1 Acute resolving form
  - 2 Destructive chronic form
- IV Vascular dermatophytids
  - 1 Migrating phlebitis (venous)
  - 2 Urticaria (capillary)

It has been shown that even a very small focus between the toes or under a toenail may result in marked generalized manifestations, and it is of no avail to attempt to treat the secondary manifestations until the primary infection is first eradicated When this site is the nails the treatment is often very difficult

DEMONSTRATION OF FUNGI

It is well to demonstrate the fungi by direct examination and culture as by this means the confusion which may arise in cases suspected of being industrial irritations is allayed and definitive treatment can be instituted A small piece of the involved eroded area is placed in 10 per cent potassium hydroxide and put in a moist Petri dish for 48 hours, after which, ex



A Tinea kerion



B Tinea circinata

Fig 214

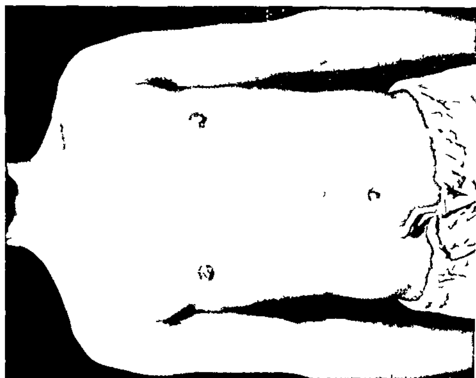




Fig 215 Tinea versicolor

Erythrasma

This can be controlled by daily washing with soap and water and the use of one of the following peeling antiseptics

7 ℞ Salicylic acid 3 0
Alcohol 50% q s ad 100 0
Sig Use twice daily locally

8 ℞ Salicylic acid 2 0
Resorcin 3 0–5 0
Alcohol 50% q s ad 100 0
Sig Use twice daily applied locally

Resistant Infections Due to Trichophyton Rubrum

9 ℞ Thymol 1 0
Salicylic acid 6 0
Benzoic acid 10 0
Lanolin
Petrolatum aa q s ad 100 0
Sig Use twice daily

10 For areas not in the groins or about the eyes
℞ Chrysarobin 0 1–0 5
Petrolatum q s ad *100 0*

11 ℞ Anthralan (Abbott laboratories) 0 2–1 0
Petrolatum q s ad 100 0

12 ℞ Chrysarobin 2 0–5 0
Chloroform q s ad 100 0
Sig Use on the feet twice daily—start with a low concentration Do not use in the groin

Onychomycosis—Tinea of the Nails

These are most difficult to cure They serve as important sources of reinfection for recurrent attacks elsewhere Pathogenic fungi can be demonstrated and grown on culture Some fungi can grow through the entire thickness of the nail and the treatment involves the daily scraping of the nail with a file or sandpaper deeply enough to insure removal of all infected parts Prescription numbers 9 10 11, or 12 can then be applied daily after each scraping operation In selected cases irradiation in fractional doses has been of help As chrysarobin is an intense cutaneous irritant it should never be applied on the face mucous membranes, or used for small children

Dermatophytosis

In this very common fungus infection, hypersensitivity is frequent and allergic manifestations, especially the dermatophytids of the hands are common This sensitivity can be demonstrated by the presence of a positive trichophyton test before the dermatophytids develop The test is carried out by the intradermal injection of trichophyton and in from 24 to 48 hours reactions of various degrees from erythema to vesicles develop at the site of injection A negative test is of diagnostic importance

Treatment of Acute Form In the acute stage wet dressings are indicated such as boric acid Foot baths are beneficial several times daily in *potassium permanganate* 1 8000 for fifteen minutes or dilute *cresolis compositus* U S P (0 5 per cent solution) Between foot baths dusting powder (prescriptions 5 or 6) can be used Schwartz (27) points out that in the presence of a high degree of sensitivity and an eruption that has spread elsewhere on the body it is not advisable to treat the primary lesion too vigorously as with the rapid killing of the fungi there is a dissemination of their toxins and a resultant intensification of the allergic manifestations In these cases *Burow s solution* or *boric acid* is the best dressing to use When there is much weeping or oozing, *aqueous tannic acid* 5 per cent may be used After the acute symptoms have subsided *salicylic acid ointment* may be applied to remove the scales

Treatment of the Subacute Form Schwartz advises ℞1 at night and in the daytime ℞2 and 3 can also be used followed by the foot powder ℞5 or 6 The author has used with exceptional results a regimen in which the patient soaks his feet each night in *permanganate solution* 1 8000 and applies at bedtime *2 per cent iodine crystals in benzol* for 3 nights followed by ½ strength Whitfield s ointment for two nights without any other treatment The whole cycle can be repeated for weeks In the case of persistence the following prescription should supplant the iodine crystals in benzol

13 ℞ Salicylic acid 3 0
Benzoic acid 6 0
Iodine crystals 2 0
Alcohol 95% ad 100 0

no recurrences The blood serologic reaction is usually positive

2 *Epithelioma* This is found later in life Biopsy confirms the diagnosis The nodules are hard and white and demonstrate central ulceration

3 *Leprosy* The pigmented spots are anesthetic There may be loss of hair in the lateral portion of the eyebrows and a fullness of the upper lid Hansen bacilli will be recovered in nasal scrapings or in tissue scrapings There may be nerve hypertrophy Biopsy may confirm

4 *Blastomycosis* Blastomyces will be found in the pus and a biopsy will confirm the diagnosis The lesions are papillomatous and verrucous and have a foul discharge

5 *Lupus Erythematosus* This occurs in young adults There is a characteristic butterfly distribution on the bridge of the nose, usually bilateral and with an elevated border

TREATMENT

Attention is paid to the general and constitutional care of the patient Some advocate the Gerson Sauerbruch diet and all agree upon mental and physical rest Local treatment is managed by electrosurgery or cautery carbon dioxide snow or the use of chemical caustics Local irradiation with the Finsen or Kromayer lamp is advocated but not all agree on the use of roentgen rays or radium therapy

Monilia Infection of the Skin

The organism usually involved is *Monilia albicans* although other organisms sometimes considered saprophytic may assume pathogenic proportions under certain conditions Thrush is an example of a monilia infection in infants affecting the oral mucous membranes The direct infections are interdigital moniliasis onychia and paronychia The allergic manifestations which may accompany these lesions are called moniliids They may develop from moniliasis of the internal organs i e stomach bronchi and lungs

TREATMENT

Internal medicaments are *potassium iodide vitamin B complex* orally and *Lugol s solution* intravenously Local treatment usually consists of soaking in potassium permanganate solution or painting with from 2 to 5 per cent aqueous *gentian violet* Ten per cent *tannic acid* is of value in the acute stages applied locally

Mycotic Granulomas

ACTINOMYCOSIS

This is commonest in the agricultural belt of the middle west and southern states It is due to the ray fungus and animals particularly cattle are susceptible The ray fungus however may be found in the oral cavity of man as a harmless saprophyte The commonest site of involvement is the jaw particulary on or just below the lower jaw In the skin blue red infiltrated nodules develop with deep induration and the formation of sinus tracts which exude pus from the ray fungus can be identified In some cases the appendix caecum, and lungs are involved the prognosis then becomes grave

Treatment

Large doses of *potassium iodide* (200 drops daily) *neoarsphenamine* and *filtered roentgen rays* are of use in localized cases Some recommend surgical treatment

BLASTOMYCOSIS

This also is commonest in the agricultural belt It begins as a papillomatous lesion which grows slowly until an elevated verrucous patch is formed It extends slowly in peripheral direction and sometimes with a central miliary abscess which can be demonstrated by the pressure of a ring curette If the pus is treated with potassium hydroxide and examined under the microscope highly doubly refractive bodies with budding forms will be found and are diagnostic *Irradiation* and *iodides* are recommended for the treatment

COCCIDIOIDAL GRANULOMA

This is a highly fatal ulcerative granulomatous condition seen mostly in the San Joaquin Valley in California The disease to some extent simulates tuberculosis After an influenza like infection which clears up after several weeks abscesses gummatous lesions or superficial granulomas may form in the skin

Treatment of Chronic Stage This requires much judgement ℞ 9, ℞ 10, ℞ 11, or ℞ 12 can be tried with caution but the last three should not be used if there are dermatophytids present These cases are best sent to a competent dermatologist who may use x ray or trichophytin therapy

Prophylaxsis After the Infection is Under Control Patients should wear wooden slippers to the showers which can be steam sterilized *Sodium hypochlorite* solution 1 per cent found in locker rooms should be removed daily and a fresh supply made, and in populous showers it should be changed several times daily, since it gradually becomes diluted to the point where it is worthless Once or twice a week the feet can be painted with ℞ 13 and a foot powder ℞ 5 or ℞ 6 used between the toes and dusted into the socks When there is much sweating frequent foot baths should be taken with 1 8000 potassium permanganate

Tinea Versicolor

Tinea versicolor is caused by the *Microsporon furfur* The spores can be easily demonstrated in scales of the lesions which are soaked in a solution of 20 per cent sodium hydroxide but they cannot be cultured

There are little or no symptoms The eruption is characterized by a fawn or brownish tinged, superficial finely scaling macule which occurs usually on the chest abdomen or back It may also be found on the axillae and shoulders it is rarely present on the face or the lower extremities There is no vesiculation or central clearing of the lesion and no distinctive border The size of the lesions vary from that of a ten cent piece to the palm of the hand

TREATMENT

The treatment consists in washing the involved areas with soap and water followed by dilute acetic acid or vinegar, and finally a 20 per cent solution of *sodium hyposulfite* or a 25 per cent solution of *sodium thiosulfate* This treatment is repeated every night for several days and is usually very successful

Lupus Vulgaris

This is the most common form of tuberculosis cutis It is a tuberculous infection of the skin with special predilection to the tip of the nose and the cheeks although it may be located on any part of the body surface or mucous membranes It occurs early in life and usually in those with a lowered resistance It is characterized by the 'lupus nodule" a pinhead size, macular or papular nodule, brown or brownish red in color, and exhibiting an apple jelly color when pressure is applied with a glass slide If the nodule is pressed with a blunt probe, the epidermis will give way easily and permit the probe to penetrate into a soft brown gelatinous tubercle



Fig 216 Lupus vulgaris

The course of the disease is chronic and ulceration and crusting is common Spontaneous central healing may result in irregular retractile scars and ectropion and other disfigurement may result The general health is not disturbed as a rule but secondary infections such as erysipelas may occur Carcinoma has been found in from 0 5 to 4 per cent of all lupus vulgaris patients

DIFFERENTIAL DIAGNOSIS

This must exclude the following

1 *Tertiary Syphilis* This occurs in adult life as contrasted to the occurrence of lupus in childhood or adolescence Syphilis is more rapid and active the lesion has serpiginous borders and the scar is smooth There are

Bones or joints may also be involved Treatment is generally ineffective Local lesions are excised Roentgen therapy is also used Iodides are ineffective See page 745 for more complete discussion

SPOROTRICHOSIS

Sporotrichosis is a chronic infectious disease characterized by the formation of nodules and abscesses which form along the lymphatics and break down in a few months Plants may be an intermediate host The disease is found in horses, dogs and rats and most cases are reported from the Mississippi River basin The gummatous form is rare in this country The lymphatic form is more common The lymphatics draining the area become indurated and a chain of nodules is seen along their course The regional lymph nodes are seldom involved Diagnosis is made by culturing the organism on glucose agar at room temperature The disease may last for years *Iodides* are specific Closed abscesses should be aspirated and iodides injected

Scleroderma

Scleroderma is a relatively uncommon condition of the skin It is characterized by a localized or diffuse induration of the skin which becomes firm thickened immobile, smooth and shiny The cause is not definitely known although endocrine disturbances have been advanced as a possible factor Two forms of the disease are recognized the *diffuse* and the *circumscribed*

DIFFUSE SCLERODERMA

This form usually affects adults and is the more serious of the two types It is not strictly a skin disease as the muscles, fascia, bones internal organs and endocrine glands may be affected by the pathologic processes of the disease (See fig 218) The onset of the disease may be insidious or relatively acute It may be accompanied by bone and joint pain and the infiltration may gradually develop on the digits nose ears and sides of the neck The patient will note an unusual hardness of the skin with a sense of stiffness or tension in making accustomed movements It may spread finally covering large areas When the disease attacks the face a mask like expression is present and the patient notes difficulty in opening the mouth widely as well as in moving the neck through its normal range of motion The initial edema of the involved skin progresses to a hard, yellow board like infiltration which tends to immobilize the joints covered Telangiectases may appear at the borders of the areas pigmentation is also common and varies from tan to deep brown in color Breathing may be difficult and chest complications are common Other complications are arthritis, endocarditis Raynaud s disease, ankylosis of extremities, abnormal calcification of the patches, ulceration over bony prominences, and atrophy of the skin

Course and Prognosis

Some patients may recover spontaneously others may succumb to pulmonary conditions or nephritis The diffuse type associated with fever and arthritic complications frequently have a grave prognosis

Differential Diagnosis

The following have to be differentiated

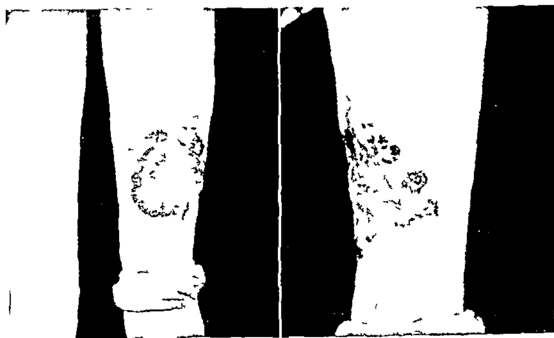
1 *Dermatomyositis* This is a rare subacute or chronic inflammatory disease of unknown etiology which follows prodromes of an infectious nature and is characterized by inflammatory thickening and edema of the skin and muscles The onset is insidious and is accompanied by fever sweating and splenomegaly The muscles of the extremities and trunk are involved and are painful and firm, or in some cases soft Recovery is rare and death usually occurs in a few months

2 *Acute Disseminated Lupus Erythematosus* This is a rare fatal systemic disease characterized by an acute onset flushed or erysipelas-like appearance of the face, edema of the cheeks erythematous lesions on the trunk and extremities ulcers and erosions of the mouth, malaise recurrent septic type fever and arthritic pains gastrointestinal disturbances lymphadenopathy, pigmentation of the face cardiac dilatation, leucopenia and thrombocytopenia with purpura

3 *Sclerema Neonatorum* This disease affects children suffering from malnutrition during the first few weeks of life It is a disease of the subcutaneous fat it appears first on the

A Actinomycosis

B Blastomycosis



C Blastomycotic dermatitis

D Blastomycotic dermatitis

Fig 217 Mycotic Granulomas

faint lilac colored border The skin is smooth shiny atrophic free of normal skin markings and the plaques demonstrate a board like induration they are firm and cannot be wrinkled

Morphea Gutta a

This is a variety of morphea and is characterized by discrete white sharply outlined papules or macules usually located on the back neck chest or wrists They vary from a pin head to a pea in size

TREATMENT OF SCLERODERMA

As the cause of this disease is unknown the treatment is purely empirical Thyroxin is suggested in the diffuse form or if hypothyroidism exists Measures to induce vasodilatation such as massage or medical diathermy are advised Other measures suggested are iontophoresis with acetylcholine fever producing vaccines supportive measures such as removal of foci of infection and exposure to ultra violet light

Precancerous Dermatoses

The cutaneous conditions considered to be precancerous are the following

- Hyperkeratoses
  - Senile keratosis
  - Senile atrophy (sailor's or farmer s skin)
  - Seborrheic keratosis
  - Cutaneous horn
  - Arsenical keratosis
- Occupational dermato es (tarm paraffin oil etc)
- Trauma and scars
- Xeroderma pigmentosum
- Roentgen or radium dermatitis
- Leukoplakia
- Kraurosis vulvae and penis
- Lupus erythematosus
- Tuberculosis of the skin
- Syphilis
- Sebaceous cysts
- Nevi
- Paget s disease
- Benign tumors

SENILE KERATOSES

These lesions are usually seen in people past middle life and occur on surfaces exposed to the elements The common areas affected are the face dorsum of the hands forearms neck and ears The growths are pin head to dime sized well circumscribed wart like dark gray or brown in color and are slightly raised, sometimes greasy but more frequently dry hard firmly adherent and when removed they present numerous horny spines on their under surface There may be some diffuse senile atrophy of the surrounding skin and while the lesions are changing into true epitheliomas some inflammatory reaction may be noted If bleeding occurs on removal of the scales the lesion has probably already undergone malignant degeneration Hazen estimates about 5 per cent of senile keratoses undergo malignant transformation

Treatment

Early diagnosis is to be desired and the lesions should be destroyed as soon as possible by electrocoagulation electrocautery or the actual cautery Before removing they may be softened by applying salicylic acid ointment for a few days Early lesions may be treated with carbon dioxide snow after curetting the surface or trichloracetic acid may be applied

SENILE ATROPHY

In this condition frequently seen on sailors or farmers the skin becomes dry thin and pigmented loses its elasticity and can be elevated in folds The hairs are attenuated and a fine scaling may be present These lesions frequently develop into low grade epitheliomata and frequently resemble xeroderma pigmentosum Senile atrophy is rarely seen in Negroes the Caucasian race especially those of fair complexion being predisposed

Treatment

The skin should be protected from the actinic rays of the sun and protective creams can be applied to counteract the dryness Small papular lesions which have persisted for several months should be considered as potentially malignant Kerato es should be destroyed by electrodesiccation

SEBORRHEIC KERATOSES

This les on usually occurs at or past middle life and is located on the back over the shoulders the chest on the abdomen at the waist

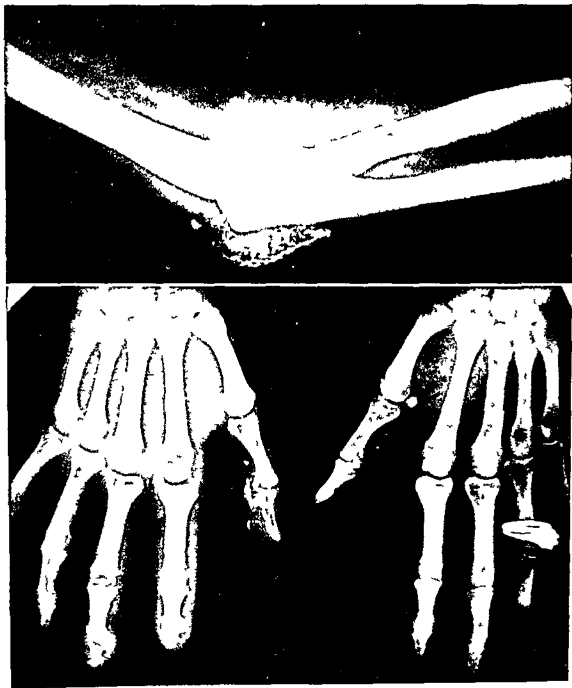


FIG 218 Scleroderma Note the Calcium Deposits in the Elbow and Hand

lower extremities rapidly extending upwards to involve the whole body The skin is waxy tense smooth, and cold to the touch

4 *Raynaud s disease* This is usually limited to the hands and feet (See page 305 for discussion)

5 *Leprosy* See page 773 for discussion

MORPHEA OR CIRCUMSCRIBED SCLERODERMA

In this form circumscribed discrete areas varying in size from a few centimeters to the size of the hand develop They are seen most frequently about the neck face forehead or breasts or along the course of the nerves The areas have a yellow or ivory color with a

faint lilac colored border The skin is smooth shiny atrophic free of normal skin markings and the plaques demonstrate a board like induration they are firm and cannot be wrinkled

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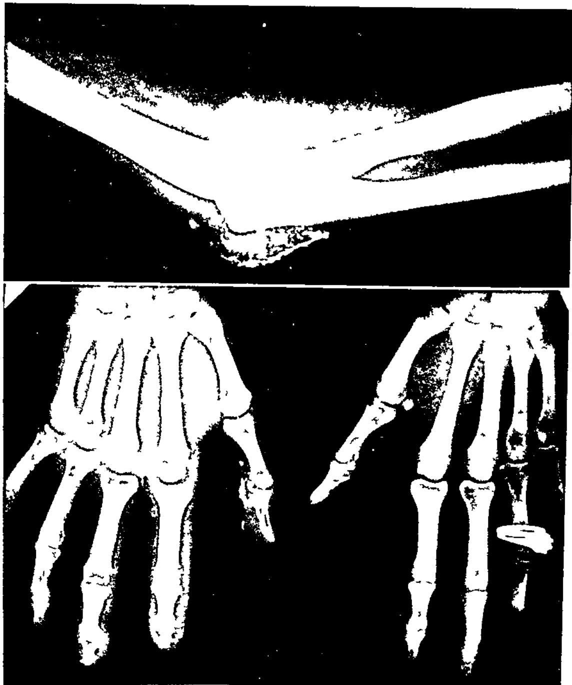


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contact with oils tars and paraffins cresote pitch asphalt, aniline and anthracene In carcinoma following a tar dermatoses there is usually a history of an acute dermatitis followed by a chronic course acneform lesions and areas of dermatitis with scars which are the site of epitheliomatous ulceration that healed spontaneously

The lesions are located mainly on the hands arms and sites of additional friction from clothing and irritation from perspiration The site of predilection of paraffin carcinoma is the scrotum from which it frequently extends to the penis and perineum

The *treatment* is chiefly prophylactic Steps should be taken to work under hygienic conditions and if necessary either discontinue contact with the offending agent or change occupation Irritated skins are treated symptomatically with bland non irritating ointments

ROENTGEN RAY KERATOSES

This lesion is seen rather frequently and occurs in chronic radio-dermatitis in the skin of both unprotected and protected operators The affected areas are sometimes associated with atrophy and telangiectasia and occasionally undergo malignant degeneration The treatment of choice for small ulcers is electrodesiccation endothermy or excision The acute dermatitis is treated with mild solutions and calamine or lime liniment Satisfactory results have been reported in treating roentgen ulcers of two years duration or more by the application of fresh *aloe vera leaf* which is cut in thick cross wise sections placed over the lesions and then bandaged with a non porous material so as to reduce evaporation The dressing is changed every three or four hours Hyperpigmentations are best left untreated as the therapeutic measures may further injure the epidermis

TRAUMA AND SCARS OF THE SKIN

Chronic mechanical and thermal trauma and irritation may alter the skin and prepare it for carcinomatous changes Epitheliomas are known to develop in old scars particularly those following burns A classical example of this is seen in Tibet where the natives make a practice of carrying portable jugs filled with glowing coals under their clothes A condition called *kangri cancer* develops The Japanese have a similar practice of carrying hot boxes with them to warm themselves during the cold season and skin cancer similar to kangri cancer has been demonstrated Carcinoma may develop in burn scars within a year of the injury and has been known to develop in Thiersch and pinch type grafts used in these cases

Treatment

Radiation therapy with heavily filtered radium is advocated as the treatment of choice in these conditions with the exception of those highly differentiated which due to their being radio-resistant are best treated by surgical procedures

XERODERMA PIGMENTOSUM

This disease is an example of actinic dermatosis which gives rise to malignant transformation It is a fairly rare disease that begins in childhood and is characterized by hyperpigmentation atrophic areas telangiectases and warty and malignant growths

Clinical Course

The first sign of the disease may be a blotchy erythema and edema which occurs a few hours following exposure to strong sunlight It persists for several days and is followed with desquamation and irregular pigmentation It is distinctly a familial disease In some cases independent of any initial erythema o edema there may be noted the development of freckle like lesions of various sizes and different shades of yellow and brown Interspersed between these lesions may be found atrophic and whitish macules the latter of which remain sharply demarcated from the pigmented areas Telangiectases and small angiomas may be present on the lips oral mucous membranes and the conjunctiva Flat or convex warty growths resembling senile keratoses al o develop and are from pea to marble size They are scattered among the pigmented and telangiectatic lesions After a few years single or multiple tumors ari e most of which are basal and squamous cell type although sarcomas angiomas and fibromas have been known to develop

Ectropion and keratitis is common The progress of the disease is slow and death from

line and sometimes on the face and neck They are round or oval sharply circumscribed elevations and vary in size from a pea to the size of a fifty cent piece They are gray brown, yellow, or black, and are greasy and freely movable over the underlying skin The greasy crust is friable and easily removed, whereupon a red granular or papillomatous base is revealed These lesions rarely undergo malignant change and are removed mostly for cosmetic reasons by desiccation When these do develop into carcinoma, it is usually of the basal cell type

In addition to the typical seborrheic wart, a hyperkeratotic seborrheic keratosis occurs in the form of a scaling pigmented patch with waxy scales, and thickened, slightly verrucous skin They are usually found on the face, scalp, and upper portion of the trunk in elderly people and are yellow, brown or black in color

Treatment

The smaller lesions should be removed by a curet If the lesions are large and numerous complete removal is not necessary They may be reduced in size and rendered less conspicuous by the application of 3 per cent salicylic and 5 per cent sulfur ointment Carbon dioxide snow is also effective if complete removal is desired Unfiltered roentgen rays may be used in doses of 2500 r with the factors 65 kv, 5 ma, 20 cm focal skin distance One exposure may be sufficient

CUTANEOUS HORNS

These circumscribed keratoses may reach considerable size and may arise from either the superficial layers of the skin or be deeply implanted in the cutis They occur usually after the fifth decade and are mainly located on the face or penis They are painless and their rate of growth varies considerable They should be examined microscopically to determine their neoplastic qualities If carcinoma develops it is usually of the squamous cell type If carcinoma is not present the lesions can be destroyed by electrocoagulation and if small, the horn can be removed with a curet after electrocoagulation

ARSENICAL KERATOSIS

Keratosis on the palms and soles associated with alopecia and hyperpigmentation of exposed parts of the body may follow the absorption of arsenicals Squamous type carcinomatous changes may follow Pigmentation is common and may present a flecked or raindrop appearance due to the presence of many small non pigmented areas Vitiligo may occur (See fig 219) The pigmentation is due to melanin and not to the deposition of arsenic Arsenic acts by intensifying the normal pigmentary mechanism since it is a strong catalyzer of oxidizing and reducing processes as well as by producing inflammatory changes



Fig 219 Vitiligo

Treatment

Electrocoagulation may be used for the treatment of the small lenticular keratoses Roentgen or radium therapy is advised for larger plaque like lesions There is no satisfactory treatment for vitiligo

OTHER KERATOSES

Keratoses may occur commonly on the lower lip They are small slightly elevated and in some cases may cover half the surface of the lip in the form of a narrow band They occur in the older age groups chiefly in males and frequently undergo malignant degeneration They should be removed as early as possible

OCCUPATIONAL DERMATOSES

Carcinomas occasionally arise from the skin alterations seen in those working in continual

chronic irritation such as observed in glass blowers and wind instrument players and irritation from badly fitting dentures seems to favor the development of leukoplakia Some believe tobacco both smoking and chewing, to be an etiologic factor in the condition Syphilis is an incidental rather than a causative factor in leukoplakia and leukoplakia is not in itself a syphilitic process It has been shown that the patches do not improve under syphilitic therapy even when active syphilis is present

Treatment

Prophylaxis is the important factor in treatment All local irritants should be avoided such as tobacco, hot and cold food, condiments, alcohol vinegar the use of hot clay pipes and ill fitting dentures Electro desiccation, the electric cautery and radium are efficient methods of direct removal Partial removal is likely to induce malignant change A bland mouth wash should be advised Roentgen ray carbon dioxide snow and chemical caustics are not advised in the treatment

KRAUROSIS VULVAE

This condition occurs in women of advanced age at the menopause or in young women who have had the uterus or ovaries removed It is characterized by a retraction of the tissues due to a sclerosing atrophy of the mucocutaneous structures of the vulva In advanced cases there is almo t complete disappearance of the labia minora frenulum and clitoris The retracted tissues may be white red or bluish in color and they usually present a glistening appearance As a rule intense pruritus is present though in some cases there is a loss of cutaneous sensibility There may be painful defecation and burning micturition

Treatment

Total vulvectomy is the treatment of choice

KRAUROSIS PENIS

This condition shows the same changes as kraurosis vulvae The shrinking process may involve the urethral orifice It is seen in elderly males who have a balanitis associated with phimo is The *treatment* is amputation of the penis and removal of the inguinal glands

LUPUS ERYTHEMATOSUS

See page 1009 for discussion

TUBERCULOSIS OF THE SKIN

Tuberculosis of the skin, especially lupus vulgaris may occasionally be the forerunner of cutaneous cancer For discussion, see page 1006 and figure 216

SYPHILIS OF THE SKIN

Carcinoma has been found in ulcerated gummas and in scars of late syphilitic lesions It has been noted that a large percentage of cases of tongue cancer are found in those with a history of syphilis Carcinoma arising from a syphilitic lesion is usually of the squamous cell type The treatment of syphilis per se, has no effect on the carcinoma, some believe that the growth may even be stimulated by arsenical therapy especially if it is located on the mucous membranes

SEBACEOUS CYSTS

Sebaceous cysts may be the forerunners of malignant degeneration Most are of the squamous cell type and are located on the face or scalp It is believed that the incidence of carcinomatous degeneration in sebaceous cysts ranges from 2 to 4 per cent Surgical excision is the treatment of choice

NEVI

Pigmented melanomas are extremely malignant and metastasize early The most dangerous mole is that which is flat slaty or blue black The e moles are commonly seen around the toes eyes and finger nails Chronic irritation trauma the application of caustics or incomplete surgical removal is the immediate cause of the malignant change Those exposed to frequent irritation should be removed by wide surgical excision or better, electrodesiccation

PAGET S DISEASE OF THE NIPPLE

This disease usually occurs on the breasts of women but some have occurred *in men It* is usually found in women over forty years of age The typical course is characterized by redness and scaling of the nipple with extension and later fissuring and crusting of the surrounding area When the crusts are removed

metastasis usually occurs by the fifteenth to the twentieth year, although death may occur *from marasmus within a few months after the* onset If the symptoms do not appear until after puberty the prognosis is more favorable as malignant tumors are less likely to develop then

Treatment

There is no satisfactory treatment The patient must be kept from exposure to the sun's rays The tumors respond well to radium or roentgen ray therapy Surgery is sometimes indicated

LEUKOPLAKIA

Leukoplakia is a chronic disorder of the mucous membranes and, as seen in the mouth, occurs as whitened areas of varying size and diverse outline There may be one or several patches on the surface of the tongue (see Fig 220), beneath the tongue, on the buccal mucosa on the gums lips and hard palate The patches are often rough later they may become fissured or ulcerated and carcinomas may develop usually of the squamous cell type There are no statistics in what proportion cancer develops

The etiology is not clearly established but



Fig 220 Leukoplakia of the Tongue with Malignant Changes

tules and papules as well as burrows which are visible on the fingers wrists, penis and axilla and a most troublesome symptom nocturnal itching The face is rarely affected except in infants The disease is spread by contact with infected persons, bed or personal clothing The *burrows* are the characteristic lesions and should be demonstrated before the treatment is commenced They are fine tortuous zig zag thready channels in the epidermis about 1 5 mm long At one end of the burrow a tiny dot will be detected, white in color and slightly distending the skin The burrow should be very carefully ruptured with a sharp pointed cannula in front of the dot and the point of the cannula gently moved to a site directly underneath the itch mite whereupon the mite will cling to the cannula and can be transferred to a glass slide and examined under the micro scope Itching rarely commences before three weeks after the infection for it requires that period for the eggs to become full grown parasites The young pregnant females spread the disease



Fig 222 Scabies

Diagnosis

The diagnosis is made upon finding the itch mite or typical burrows It should be regarded as highly probable when the patient gives a history of itching when he is warm in bed and a localization of the lesions on the thin skinned portions of the body such as the webs of the fingers, glans penis buttocks, axillae and flexor surfaces of wrists and fore arms or the breasts and nipples in women In babies the lesions should also be sought on the palms and soles Other presumptive evi dences are a history of the disease in another member of the family, and the absence of lesions on the face and scalp In persons of hygienic habits the diagnosis may be difficult, but the burrows should be carefully sought for and as a *rule* diligence will be rewarded.

Treatment

Certain newer refinements in the treatment of scabies have appeared in the past few years They are *Sulfur Foam* (Wyeth) and the use of *rotenone* marketed under the trade name of *Rotenone* (1–2 per cent) They are applied locally and are non irritating Other standard treatments are the one day *Danish ointment cure* and *sulfur ointment* (3–10 per cent) which is applied for three successive nights after a hot bath and a thorough scrub with soap and water which is repeated on the fourth night



Fig 271 Lupus Erythematosus

red oozing eroded areas are revealed The inflammatory area is well defined and when advanced can be easily palpated it has the feeling of a large sized button in the substance of the areola and adjacent parts The nipple become flattened and retracted and later carcinomatous infiltration occurs in the involved breast tissue In advanced cases the disease may spread to the thorax abdomen and axilla The disease is usually unilateral and there may be a serous exudation from the nipple

Treatment

Paget s disease of the breast requires surgical removal of the mammary gland and accompanying lymph nodes

Animal Parasitic Skin Disorders

SCABIES

This disease sometimes called the Itch, is the commonest of all skin diseases caused by animal parasites It is highly contagious and is characterized by discrete excoriations pus

evenly Treat the seams of the inside of the shirt and trousers in a similar manner Also dust the powder lightly in the bedding between the sheets and blankets and on the mattress About one ounce of powder or one half of the contents of the can will be necessary for one application

The lice eggs or nits are not destroyed by DDT but action of the powder remaining on the clothing will kill the lice as they hatch from 3 weeks up to a month after the initial treatment It will be necessary however to reapply the powder to the underwear as it is changed until it is certain that all the lice have been destroyed Those who have mingled with the patient or who have lived in his quarters should apply the powder in the same manner as a protective measure The patient s living quarters should be sprayed with a 5 per cent DDT solution every 2 or 3 days for 10 days after the last lice and nits have been seen

Pediculosis Pubis

The crab louse is found attached to the hair of the pubis armpits or eyebrows and in some cases are found on the thighs and legs as well It is commonly transmitted by sexual intercourse or from a toilet seat Nits will be found attached to the hairs and examination will disclose scratch marks blood crusts and blue colored macules caused by old bites

Treatment The following can be applied locally The use of blue ointment is to be deprecated as it frequently causes a dermatitis and there is little need to prescribe such messy treatment

1 Cuprex ointment (Merck)
2 Tincture of larkspur
3 2 per cent ammoniated mercury ointment
4 Balsam Peru
5 ℞ Carbon tetrachloride C P
   Betanapthol aa 10-20 per cent
   Petrolatum q s

It may be well to repeat the treatment in fourteen days to destroy all crabs who have resisted the first course of treatment It is well to shave the pubic hair before beginning treatment Underwear and linens should be boiled

Disinfestation with DDT Sprinkle DDT powder in the pubic and anal regions in the armpits and in all other hairy areas of the trunk arms and legs In hairy individuals the best policy is to apply the powder over the entire body from neck to feet Rub the treated areas so that the powder will sift down to the base of the hair where lice and eggs are found About 10 grams (⅓ of a can) of powder will be required for the average infestation The patient should not bathe for 24 hours A second application of DDT powder after 7 or 10 days is essential to kill lice hatching from eggs Men exposed to infested individuals should use DDT once as described for protective purposes Also toilet seats should be wiped with the DDT insecticide solution

Cimicosis (Bed Bug Bites)

Bed bugs or *cimex lectularius* frequent the joints of beds the seams and edgings of mattresses the cracks of the floor or behind the panels or wallpaper They only appear during the night and bite the exposed parts of the skin The lesion usually has a punctate center and is sometimes arranged in groups of three Treatment consists in a thorough disinfection of the premises with hydrocyanic acid or a strong solution of corrosive sublimate applied to the infected crevices of the floors and furniture The itching can be alleviated by bathing the affected parts with alcohol The bugs will not come out in the light and by sleeping with the light on the bedbugs can thus be outwitted

Bedbug Control with DDT

DDT has proved highly successful in the control of bedbug infestation Spraying with 5 per cent DDT in crude kerosene will destroy bedbugs within twenty four to forty-eight hours Also bedbugs entering the sprayed area within six months after its treatment will be killed About 220 c c of solution is the average amount required for one bed mattress springs bed frame and pillow A compressed air paint type spray outfit is the most satisfactory equipment for dispensing the solution Workers should wear masks of the filter type or of moistened fine gauze over the mouth and nose Smoking should be prohibited in the room until the following day

To avoid irritation the patient should be cautioned not to repeat the treatment without consulting his physician Infants are treated by rubbing 10 per cent Balsalm of Peru in vaseline into the affected areas

The author has had success with a new preparation *benzyl benzoate emulsion* (Burroughs Welcome) The patient soaks in a hot bath after which he is washed thoroughly with soft soap but not scrubbed After drying the benzyl benzoate is applied all over the body except the head and neck After the solution dries the patient is allowed to don clean pajamas while his clothes are being disinfected He is allowed to return to duty on the morning of the third day A few patients note a stinging sensation or some dryness but it rapidly disappears following the application of calamine lotion This treatment is ideal for Service personnel where the object is to return the patient to full duty as soon as possible

PEDICULOSIS

There are three species of lice that affect man, the *Pediculus capitis, corporis* and *pubis*

Pediculosis Capitis

This is found chiefly in women and children with long hair Frequently scratch marks will be found on the neck and shoulders where the insects fall from the hair Transmission is from hats combs fingers, etc A search *will reveal the nits which are small, shiny,* oblong pearly bodies attached to a hair at an *acute angle* Careful combing of the hair with a fine comb will reveal the translucent gray colored lice

Treatment *Tincture of larkspur* or a mixture of equal parts of *kerosene* and *olive oil* is applied to the hair in the evening The head is wrapped in a towel and in the morning the scalp is thoroughly shampooed with green soap after which the hair is wet with *vinegar* or 6 per cent *acetic acid* and the nits combed out with a very fine comb

A scalp lotion that has been highly successful in the treatment of pediculosis capitis has the following formula

Phenyl cellosolve	40%
Ethanol	30%
Water	25%
Methyl salicylate	5%

Sig Apply locally to scalp

Disinfestation with DDT The patient should dust his hair with DDT powder and rub it in thoroughly He should also apply the powder in all his caps and hats At least one additional application should be made from one week to 10 days later in order to kill all lice hatching from eggs The head should not be washed for at least 24 hours after each treatment Men who have been exposed to persons infested with head lice should use DDT powder once in the manner described as a protective measure

Pediculosis Corporis

This infestation is most common in old people who are careless in their body hygiene and in vagabonds who bathe infrequently It was quite common among the soldiers in the last World War There is a generalized itching with parallel scratch marks on the shoulders and in old cases hyperpigmentation and erythematous macules The louse lives in the seams of the clothing and feeds on the skin where the clothing touches the body The insects are detected on the inner lining of the underclothing as soon as they are removed rarely are they found on the skin itself This condition is differentiated from scabies in that the hands and feet are free, and there is a predilection for the upper back, or interscapular space

Treatment

1. A thorough bath with sponge and benzine
2. *Boil all the underclothing*
3. If there are nits in the hair they should be destroyed as described for pediculosis capitis Hair with nits should be removed
4. NCI powder of value—naphthalene 96 per cent creosote 2 per cent and iodoform 2 per cent
5. Disinfestation with DDT The infested person should first take a hot soapy bath and then disinfect his clothing and bedding with DDT powder which should be prescribed in 2 ounce sifter top cans The method of application is as follows The powder should be liberally applied over the entire inner surface of the underwear paying special attention to the seams As the powder is applied, rub it in lightly by hand to spread it

evenly Treat the seams of the inside of the shirt and trousers in a similar manner Also dust the powder lightly in the bedding between the sheets and blankets and on the mattress About one ounce of powder or one half of the contents of the can will be necessary for one application

The lice eggs or nits are not destroyed by DDT but action of the powder remaining on the clothing will kill the lice as they hatch from 3 weeks up to a month after the initial treatment It will be necessary however to reapply the powder to the underwear as it is changed until it is certain that all the lice have been destroyed Those who have mingled with the patient or who have lived in his quarters should apply the powder in the same manner as a protective measure The patient s living quarters should be sprayed with a 5 per cent DDT solution every 2 or 3 days for 10 days after the last lice and nits have been seen

Pediculosis Pubis

The crab louse is found attached to the hair of the pubis armpits or eyebrows and in some cases are found on the thighs and legs as well It is commonly transmitted by sexual intercourse or from a toilet seat Nits will be found attached to the hairs and examination will disclose scratch marks blood crusts and blue colored macules caused by old bites

Treatment The following can be applied locally The use of blue ointment is to be deprecated as it frequently causes a dermatitis and there is little need to prescribe such messy treatment

1 Cuprex ointment (Merck)
2 Tincture of larkspur
3 2 per cent ammoniated mercury ointment
4 Balsam Peru
5 ℞ Carbon tetrachloride C P
   Betanapthol aa 10–20 per cent
   Petrolatum q s

It may be well to repeat the treatment in fourteen days to destroy all crabs who have resisted the first course of treatment It is well to shave the pubic hair before beginning treatment Underwear and linens should be boiled

Disinfestation with DDT Sprinkle DDT powder in the pubic and anal regions in the armpits and in all other hairy areas of the trunk arms and legs In hairy individuals the best policy is to apply the powder over the entire body from neck to feet Rub the treated areas so that the powder will sift down to the base of the hair where lice and eggs are found About 10 grams (⅛ of a can) of powder will be required for the average infestation The patient should not bathe for 24 hours A second application of DDT powder after 7 or 10 days is essential to kill lice hatching from eggs Men exposed to infested individuals should use DDT once as described for protective purposes Also toilet seats should be wiped with the DDT insecticide solution

Cimicosis (Bed Bug Bites)

Bed bugs or *cimex lectularius* frequent the joints of beds the seams and edgings of mattresses the cracks of the floor or behind the panels or wallpaper They only appear during the night and bite the exposed parts of the skin The lesion usually has a punctate center and is sometimes arranged in groups of three Treatment consists in a thorough disinfection of the premises with hydrocyanic acid or a strong solution of corrosive sublimate applied to the infected crevices of the floors and furniture The itching can be alleviated by bathing the affected parts with alcohol The bugs will not come out in the light and by sleeping with the light on the bedbugs can thus be outwitted

Bedbug Control with DDT

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TABLE LXI

Differential Characteristics of Common Allergic Dermatoses

(After Sulzberger, Goodman, and Coca)

Contact Dermatitis	Atopic Dermatitis	Drug Eruptions	Fungus Dermatitis—Eczematous Dermatophytids
Epidermis is shock tissue and is practically always the only tissue affected	Blood vessels in cutis is the shock tissue. Capillary permeability and smooth muscle spasm	Deep cutis, cutis, epidermis and follicles are shock tissue	Upper cut[illegible] c[illegible]ti
Rarely a family history of asthma, hay fever or atopic dermatitis. If these are present they are coincidental	*Family history of asthma, hay fever and perhaps* migraine or urticaria	Same as contact dermatitis	
Lack of personal history of above	Personal history often reveals some of those der[illegible]ab[illegible]e	Same as contact dermatitis	
Eosinophilia rarely demonstrable	Eosinophilia in blood smears	Eosinophilia in blood smears	
Scratch and intracutaneous skin tests are negative	Scratch and intradermal tests positive	In the urticarial eruptions the scratch or intracutaneous tests are positive	Intracutaneous or patch test
Passive transfer—negative	Passive transfer—positive	Same as contact dermatitis	
Relief on removal of offending agent	Same	Same	May be desensitized by fungus extracts
Recurrence on [illegible] exposure	Same	Same	*Recurrence on re[illegible]fect*
Identification of offending substances by production of eczematous reaction to patch tests. Reaction time 24 or more hours	Offending substances cannot be identified by patch tests. Reaction time five to thirty minutes	Patch test usually produces the eczematous reaction in *eczematous drug eruptions* but rarely reproduces the morphology of the dermatosis in a [illegible] form or vegetating drug eruptions (Dermatitis medicamentosa). Reaction time one minute to days	Intracutaneous or patch test is specific but not *diagnostic*
Presence of purely epidermal [illegible]—very thin dermal [illegible] (to bullae) papules. Histology: spongiosis	Presence of capillary hyperpermeability. Papules, lichenification and [illegible]	Lesions often characteristic of offending drug. Bromides and iodides cause a form vegetating or nodular-like and erythema-like eruptions. Phenolphthalein, antipyrine, etc. produce fixed drug eruptions	Vesicles located usually in upper cutis and cutis. Larger than those of contact dermatitis. Frequently they [illegible] distinguishable
Causal substances are allergens but not atopens—rarely proteins but [illegible] chemicals, metals, salts, [illegible] plant products [illegible]	Causal substances are atopens, reagins or antigens but not proteins. Usually foods, inhalants (powders, dust, animal emanations, spores of fungi, plant pollen). Clothing—silk, wool, dander	Allergens but not atopens or antigens	Allergens—fungus products (hyphomycetes and molds)

ECZEMATOUS CONTACT DERMATITIS

This condition also called *dermatitis venenata* or *dermatitis medicamentosa* is an inflammation of the skin due to the continuous or intermittent contact with an allergen or cutaneous irritant Today eczematous dermatitis is considered an allergic disease Many factors are regarded as playing a role in the disease complex Among them are the hereditary, seborrheic pyogenic, bacterial psychic neurogenic allergic icthyotic and metabolic factors Common allergens met with in occupations and drugs with their characteristic type of eruptions are discussed in the chapter on Allergy

Common causes of dermatitis venenata are *poison ivy, poison oak sumac acids alkalies, antiseptics primroses ragweed tomato plants geranium chrysanthemums liniments* and *dyes* Miscellaneous causes of contact dermatitis are hair dyes, clothing dyes depilatories nail polishes cosmetics adhesive plaster shoes dress shields gloves furs and hat bands

This history is a very important part of the diagnosis and is well worth any time spent upon it See figure 196 for contact areas

General Management of a Dermatitis

1 The cause should be sought and removed at *once* If the dermatitis is acute soothing preparations should first be used

2 The dermatitis should be cooled off with either colloid baths (see skin formulary page 1028) or 0 5 per cent aluminum subacetate wet dressings

3 After the above medication it is best to keep the skin from drying out too much between treatments The following should be applied to the area all three being equally satisfactory

a Lassar s paste without salicylic acid
b Boric acid 1 5 Ung Aquae Rosae 30 0
c Zinc oxide ointment diluted with yellow petrolatum

4 As the dermatitis continues to subside the medication may be changed to calamine lotion with zinc oxide followed by any of the three lotions mentioned in (3) above Another preparation of merit is 3 per cent *icthyol* in *zinc oxide*

5 As the dermatitis continues to subside stronger and more stimulating applications are used particularly if there is a tendency to become dermic First use 1 per cent *picis liquidis* and *salicylic acid* in zinc oxide ointment This may be increased gradually to 10 per cent although 3 to 5 per cent is the usual limit If this is well tolerated 1 to 2 per cent *crude coal tar* may be applied If this is tolerated tar together with ultraviolet light may be given

6 If infection is present in the early stages 1 8000 *potassium permanganate* dressings should be applied

7 A diet which omits the common irritants such as cheese eggs berries, nuts tomatoes chocolate, white bread sea foods and pork should be prescribed

Method of Patch Testing in Cases of Weed Dermatitis

Common offenders are the short ragweed giant ragweed burweed cocklebur marsh elder and gaillardia The suspected plant should be placed after being dried in a jar, covered with ether and allowed to stand for 24 hours The ether is poured off and allowed to evaporate A tarry residue will be left This is diluted one part to ten of ether and bottled it will keep for years in this state ready for use To apply the vial is tilted and the cork moistened and applied to the skin of the back abdomen or thighs As a rule positive tests appear within an interval of from 6 to 48 hours The reaction is a localized erythema with edema and vesiculation Testing should be delayed until the dermatitis has subsided Trumell (28) suggests a method of desensitization 1 gram of the tarry residue is dissolved in a small amount of ether it is then added slowly to 100 c c of cottonseed oil and mixed heated in order to drive off the ether and bottled in dropper bottles The patient is given 5 drops three times daily in milk through a straw

Since there is no controlled evidence (35) that the daily ingestion of small amounts of extract over a long period of time will modify the dermal test or give protection and the ingestion of large doses within a period of a few months is still experimental the method of choice if one must immunize against ivy appears to be by inoculation with repeated doses of extract begun well before the season

and increased in strength at frequent intervals, within the tolerance of the patient This *appears to be the method of choice, not because* it is believed that the experimental evidence is wholly satisfactory, but because the favorable statistical evidence outweighs the unfavorable

Protective Ointments for Poison Ivy

For those who work about areas where poison ivy, *poison oak or sumach, is common the* following ointments are suggested Since these ointments will only neutralize as much poison ivy as the quantity of available oxygen on the skin a thick layer of the ointment is advised

Formula 1

℞ Castor oil	21 5
Olive oil	21 5
Lanolin anhydrous	21 5
Diglycol stearate	12 9
Paraffin refined	8 6
Boric acid	2 0
Sodium perborate	10 0
Duponol WA pure	2 0

This has a greasier base than Formula #2 but is more stable in summer heat

Formula 2

℞ Cetyl alcohol	35 1
Stearyl alcohol	5 3
Ceresin	3 5
Castor oil	20 8
Mineral oil	21 9
Duponol WA pure	1 7
Sodium perborate	10 0
Boric acid	1 7

This must be stored in a cool place until used

Clothing must be removed after exposure before the ointment has been washed off otherwise the unprotected skin may be exposed to contaminated clothes Before the clothes are worn again, they must be decontaminated as should *also tools and instruments which have* been used in cutting poison ivy Decontamination can be effected by washing or immersing them for from 15 to 20 minutes in a one per cent solution of *calcium hypochlorite*

Management of Rhus Dermatitis

It is sometimes satisfactory to wash the affected area with brown soap and water and to rinse and sponge it with alcohol if this can be done within the first four hours after contact with the poison ivy Otherwise the treatment advised is a 1 per cent aqueous solution of *zinc sulphate* which is patted on daily for one week This is then followed by a similar application of the following prescription

℞ Resorcinol	7 0
Glycerin	10 0
Bis subnitrate	30 0
Pulvis amyli	30 0
Dist water q s ad	*360 0*

Sig Pat on daily three times to involved areas

If later there appears to be excess drying, mineral oil may be applied Other standard recommended treatments are continuous wet dressings of 1 4000 *potassium permanganate* or 1 per cent *aluminum subacetate,* or 10 per cent *ferric chloride* in calamine lotion

The treatment of acute ivy rashes with ivy extracts should be discouraged, because many patients are made worse and there is no satisfactory evidence that any are helped

The data offered in the literature are not convincing in regard to the phylactic value of treatment with antigens of ivy orally or parenterally Ivy dermatitis is a self limited disease of short but indefinite duration with variable s*ymptoms, and no satisfactory* evidence has been brought forth to show that the course has been changed for the better by this therapy Since it is known that many patients are made worse because severe reactions occur when large doses of extracted solids are injected and since the practice is not in conformity with theory it is believed that the treatment of acute ivy rashes either parenterally or orally with ivy extracts should be vigorously discouraged

Atopic Dermatoses

This condition is seen in infants, children and adults It is commonly called infantile *eczema and in adults is recognized by many* skin authorities as adult manifestations of infantile eczema

The essential cause is unknown There is usually a history of familial atopy, such as asthma, hay fever, migraine or eczema In infants it is commonly seen on the flush areas and may be widespread There is no characteristic distribution in early childhood but in adult life the picture is characteristic The face, neck antecubital and popliteal

spaces are affected In the infantile cases such agents as milk eggs and oatmeal are believed to be causative factors Exciting factors are exposure to heat sun wind strong soaps dust wool and silk and sometimes furs The affected skin is rough red and fissured or cracked It may ooze serum and the child is fretful from the constant itching

In older children the condition may appear as a papular form on the extensor surfaces of the extremities or as a lichenoid variety which is characterized by small discrete flat brownish papules which later become confluent and are principally seen in the antecubital and popliteal areas This lichenoid variety is the form commonly seen in adults These patients become easily sensitized and if they are not treated vigorously early in life may develop multiple sensitivities

TREATMENT

In infants the skin should be kept clean soap should be omitted from the baby s toilet Instead starch oatmeal or bran baths should be given daily with mineral or olive oil as cleansing agents The allergic infant is probably only sensitive to foods and usually does not acquire a sensitivity to wool silk and bacteria until after one year old Boiled or evaporated milk can be substituted for cow s milk Soy bean milk is a good preparation and can be purchased as *Sobee* (Mead Johnson) or *Mull soy* (Borden) Card board splints can be made for the child or he can wear a soft muslin mask to aid in preventing scratching Orange juice and cod liver oil are best discontinued during the period of food trials Crystalline vitamins A and D may be given during this period as well as corn meal or rice as a cereal

In older patients topical remedie are useful for the itching and discomfort Some preparations which have been recommended are *aluminum subacetate* ½ to 1 per cent *crude coal tar* ointments *or liquor carbonis detergens* Soaps should be discontinued and can be supplanted by sulphonated oils The *elimination diets* as suggested by Rowe should be tried *Sedation* with the barbiturates may be necessary As with many other skin diseases the value of a careful history and an appraisal of the environment of the patient cannot be overestimated

Physical Therapy in Dermatology

In a recent paper (29) Robinson has stressed that being an accredited M D is not sufficient justification for the use of such apparatus as roentgen rays electrodesiccation electrolysis and ultraviolet light without proper training in their use He believes that all who use such apparatus should (1) know the apparatus which is to be used (2) know for what diseases it should and should not be used and (3) know the diagnosis of the condition which is to be treated

The following tables show the indications and the contraindications of such apparatus in the field of dermatology Because they are indicated is no guarantee that a cure will follow In all cases if the etiologic factor is known it must be removed or perhaps receive additional local treatment

Cryotherapy in the Treatment of Common Skin Diseases

Carbon dioxide snow therapy was first introduced in 1905 by Pusey but it has never achieved the popularity some think it deserves This has been partially due no doubt to its being difficult to obtain and to the cumbersome equipment needed Recently small portable outfits have been described in the literature (30) (31) (32) which are low in cost and can be carried in the medical bag See figure 223 These outfits comprise a small expansion chamber a set of plastic crayons of various sizes and a central pestle as an aid in tamping the snow into a compact mass and thus insuring an invariable size of the active tip The operator s fingers are protected at all times and there is no danger of small chips of ice coming off and injuring the nearby tissues

Carpenter (30) has called attention of always using a watch with a second hand as the time element is very important All old scales or crusts are removed before the treatment which insures a more uniform penetration of the cold Freezing may extend beyond the circumference of the applicator and for this reason a crayon should be selected which is smaller than the lesion to be treated



FIG 223 Portable Cryotherapy Outfit
(Specialties Mfg Co Bloomfield N J)

Uses	*Rema ks o the Treatm t*
Acne (33) (34)	A sl sh of c bon d o d tone a d *flowe s of sulf h s be n found of al e* It is appl ed o or tw weekly Con t und ted n Neg oes d in ly post rad t onc s
Ang omas	Sp d ne us of ad lt usu lly on th f e will espo d to one ten ec d treatm t sing mode ate pre e
	A g om of fa cy elv espond It s ggested th e tri l t atm t from t n to th ty s o ds d tio u ing light p ess e r ord
	Simplex type— e fi to te onds w th m der t pr
	Ca nou typ (le th 2 cm)— fi e to ten s co d w th he y p e su
	Do t u e f llow g rad m the py
Corns—Call es	Apply sal cyl c ac d plast (20–40 p t) for 48 hou bef e pply g CO ow for 40 to 60 sec nds w th hea y p s re
Keloids (F llowing acn)	*L bea y pr su lo f om l t 60 s d* d pend g p th th kne f th scar
L ch n Plan s	Of e n th form (hyp t oph) f d o the m ddl th d of the l g Mod t pr ss re w th f e gs of 15 s ds ecomm nded
L p s Ery th ma tosu	*F i l l will d appe r u ng med um* p e u d f m 20 t 40 second time A mooth ar w ll foll w
Molluscum Conta g o m	40 se onds w th h avy pres re recom m nded if ly f w ar prese t
Na	O ly the h ry pap llary erruc f rm o m e sk typ s sh ld be tre ted w th CO_2 s ow Start w th ten eco d l ght press e and g ve se er l t tme t rath r th one d tru t e tre tment
Rosa ea	L ght press f fi e co ds o er the l ed eas w ll red ce the edn s
	Ca pe te (30) lls the pe cil d w ys er th heek f the are l e
S nile K atos	M d m p e s e fo from 30 to 45 ec ds ecommend d
Tub los C t s	T e tm nt ri w th th k f the l b t espo s f o ble
Ve ruca	B t e lts w th ommo flat a d pl tar wa t H y p e f f om 30 to 60 s f th e mm wa t *Pl tar* w t h ld fi t h e a l cyl c ac d pl ster ppl ed fo 48 h Aft p r g aw y th k n CO_2 h ld be pplied w th he vy p es e f f om 45 to 90 se d Small fl t wa t w ll d ppe r w th med m p f r fr m 2 t 5 *s ond f r ne o two t tme t*

TABLE LXII

Roentgen Ray Therapy in Dermatology

(After Robin on)

I d cated	Contra d cated	Questionable
Tempo ry h ir epilation (ringworm t atment) 1 d	In p ev ously ir adiated pat ents	Seborrh a cca (scalp)
Sebo hea d rmat tis 4 x —1 e d	F perma ent ha ep lat on (perma n nt sc s nd t lang ectasia result)	Sebo h d rmat tis (scalp)
Atop e zema (eful only a few exposu small doses Elimin tion of c se ne essary)	N vu vasculosus	Pity as s osea (o ly symptomatic t tment— few exposures will sho ten d tion
Ep dermophytosis— cut edemato s ph se 4 e — 1 e d	A om	Hype hidro is (esult not permanent)
Blastomy os 8 —3 d	Rosa ea	Lupus vulga is
Acti omyco 8 x —3 e d	V ruca cam ta (o g n tal r g n— rea t n o gon ds)	Lupu vulg is scr fuloderma
G an lom fung ides 20 e —3 d	Lipom	Lupus erythem tosus
Acn vulga 24 x —3 e d	F b oma	H rpes s mplex
V rr a v lga (when isol ted or ngl) 3 — 3 e d	Thos w th blood dyscra ia (nem a tc)	H rpes zoster
Lymph blast m nd leukemia (f r l f tem po ar ly) 0 —5 d	P lech (t eat th cause)	P u go nod la
Psoria is (l l m ted l nd t n ecurr t) 4 e —1 d	T be rs l	Impetig contag osus (when other m ns f l)
Keloid (y ng) 4 e —1 e d	Lupu rythematos s	G n loma ingu n l (f n v l)
Skin p (n ca oma o h pes zost) 3 ex —1 e d	Pemph gu	Keloid (ld)
G nuloma a nula 6 x —1 e d	De mat tis He petif rm	Foll ul t (t eat ca se)
Ep th l oma 10 x —5 d	Parapso iasis	P y hia— t ophy of nail
F u l 2 —5 d	Cla u	L hen planu
Ca b n le 2 x —1 e d	Callos ta	Erys pelas (ulf n m des p f abl)
Pru tis a nd vul (few t e tm nt) 8 e — 1 d		O y bomy os
Rhu d rm t t s (a t l lly) 4 x—½ e d		Coc d l gra ulom
P ty ia s osea 4 e —½ d		Pru t s (em cause)
Sy os ulgari 8 x —1 e d		Scl roderma
G a l m pyog um fte des at n 6 ex — 3 d		
Tin ba bae (t nea y os) 8 e —1 d		

d rythem doses e pos s (t atm nt)

TABLE LXIII

Ultraviolet Irradiation

I d cated	Contra nd cated	Questionable
Lupus vulgaris (with pressure)	Those with idiosyncrasy to the actinic rays	Rosacea
Alopecia areata	Miliaria rubra	Infantile eczema
Psoriasis (sub-erythema dose)	Xeroderma pigmentosum	Eczema (neurodermatiti) may be come irritated
Pernio	Hydroa vacciniforme	Eczema seborrheicum (may become irritated)
Frost bite (sub-erythema dose)	Acne keloid	Acne vulgaris (may help)
Roentgen ray dermatitis (erythema dose)	Lupus erythematosus	Epidermophytosis
Infection eczematoid dermatitis	Herpes simplex	Rhus dermatitis
Pityriasis rosea (erythema dose)	Urticaria	Parapsoriasis
Acne vulgaris	Tinea versicolor (vitiliginous type)	Erysipelas
Sycosis vulgaris	In those taking sulfonamides	
Paronychia		
Erysipelas (erythema dose)		
Wounds sluggish		

Indications for Electrolysis

1 Hypertrichosis
2 Nevus pigmentosus
3 Nevus araneus
4 Dilated vessels in telangiectasia and rosacea
5 Lupus vulgaris
6 Sebaceous adenoma
7 Tricho-epithelioma



Fig 224 Note How the Elastic Crayon Protects the Operator's Fingers

TABLE LXIV

Electrodesiccation

Indicated	Contraindicated	Questionable
Nevus pigmentosus (mole)	Chancroid	Xanthelasma
Nevus unius lateralis	Angioma cavernous type	Verruca palmaris et plantaris
Verruca vulgaris		Lupus erythematosus (discoid type)
Verruca filiformis		Molluscum contagiosum
Verruca accuminata		Angioma
Leukoplakia		
Lupus vulgaris		
Epithelioma basal cell type		
Seborrheic keratosis		
Senile keratosis		
Roentgen ray ulcers		
Rhinophyma (to reshape nose)		
Granuloma pyogenicum		
Granuloma inguinale (small circumscribed lesions)		
Keloid (followed by roentgen ray irradiation)		
Cornu cutaneum		

Skin Formulary

Alkaline Laxative

℞ Fldxt Cascara aromatic	16 0
Syrup Rhei Potassii Comp	90 0
Magna Magnesia q s ad	240 0

Sig Teaspoonful to desertspoonful t i d a c

In larger doses the above is efficient without cascara and it may be given in urticarias with gastrointestinal symptoms and hyperacidity simply for its alkalinizing effect Dose 1 tablespoonful three times daily

Alkaline Laxative without Cascara This is a semi routine measure when alkalinization with catharsis is required such as in toxic erythemas or exfoliative accidents following arsphenamine administration

Aluminum Subacetate Solution Full strength is 8 per cent It is diluted with water 1 16 and used in 0 5 per cent solution If there is a cloudy suspension or precipitate it is unsatisfactory

Uses It is used in acute weeping dermatitis or oozing eczemas The dressing should be kept soaked all the time since damage may result from drying Covering with oiled silk will prevent drying One can alternate with Boro ointment or zinc oxide ointment diluted with petrolatum

Asiatic Pill Ingredients are arsenic trioxide and black pepper in varying proportions The Parke Davis product is the best (grain $\frac{1}{2}$ as trioxide) It may be used from months to years without arsenical symptoms

Dose One to three pills three times daily

Boro Ointment

Boric acid	1 5
Ung Aq Rosae	30 0

Sig Apply locally for bland lubricating effect

Uses This is a good preparation either alone or with calamine when crusting present It is irritating to some skins and inferior to the simple Ung Aq Rosae or zinc oxide

Balsam Peru

Balsam Peru	5%
Petrolatum q s ad	30

Sig Apply locally once daily

Uses Stimulant to indolent wounds or ulcers in order to promote granulations or scars

Calamine Liniment

℞ Olive oil	30 0
Tragacanth	4 0
Oil of rose	0 5
Oil of lavandulae	0 5
Phenol and glycerine	0 5
Calamine	30 0
Zinc oxide	30 0
Distilled water q s ad	480 0

Sig Apply three to four times daily generously Don t rub in

Note This does not produce as much drying as calamine lotion If desired to increase the antipruritic effect camphor phenol and camphor or camphor chloral 10 to 30 minims to the pint may be used In large amounts cotton seed oil may be used

Uses Extensive subacute dermatitis poison ivy vesicular dermatitis and dermatitis herpetiformis In vesicular dermatitis the lotion should be used preferably in combination with Boro In dermatitis herpetiformis sulfur 0 5 to 1 per cent may be added The liniment should never be used on the scalp

Calamine Lotion

℞ Zinc oxide	30 0
Glycerin	0 25
Calamine powder	30 0
Liq phenol	0 25
Aqua q s ad	480 0

Sig Shake well sop on 4 or 5 times daily and allow to dry

Uses Acute dermatitis not accompanied by oozing or crusting It should NEVER be prescribed alone owing to its drying effect The skin should be lubricated once or twice daily to prevent fissuring

Castellani Paint

℞ Saturated alcoholic sol basic fuchsin	10 0
Aqueous sol phenol 5%	100 0
Boric acid	1 0
Acetone	5 0
Resorcin	10 0

Sig Paint locally twice daily

Directions Mix and filter saturated alcoholic solution of basic fuschin and aqueous solution of phenol 5 per cent and add boric acid After two hours add acetone and after two more hours add resorcin

Calomel Dusting Powder

℞ Calomel	4 0
Boric acid	4 0
Pulv talc	20 0

Chrysarobin

℞ Chrysarobin	0 6
Ung Zn oxide	30 6

Sig Rub in locally ONLY on the affected part once daily

Caution—chrysarobin is an intense cutaneous irritant and therefore should never be applied to the face or scalp It is occasionally used in ringworm of the scalp by some dermatologists (5 to 10 per cent) The patient should be cautioned that his underwear will be stained a permanent purple If it causes dermatitis, calamine lotion should be applied It should never be used on acute or rapidly spreading psoriasis, as it may cause an exfoliative dermatitis It must never be employed in an unknown case, or on small children

Colloid Bath One or two cups of oatmeal are boiled in 2 quarts of water and strained through cheese cloth When cold, one cup of baking soda is dissolved in the gruel Stir this mixture into a bathtub full of water as hot as the patient can comfortably stand The patient should soak in the tub for from ten minutes to two hours In order to prevent cooling, the tub should be covered with a blanket On leaving the tub the patient dries himself by patting not rubbing and should allow some of the bath mixture to dry on his skin A fatty preparation should always be applied to the skin in order to keep it soft and prevent its becoming too dry For this purpose Lassar s paste without salicylic acid may be used Boro or a mixture of equal parts of glycerin and olive oil to which is added oil of bitter almonds, 0 25 c c to the ounce, is also satisfactory

Uses Bath and winter dermatitis and pruritus, generalized dermatitis and patchy exfoliative dermatitis It is not used locally for small lesions

Crude Coal Tar

℞ Crude coal tar	3 6
Burrow s sol (filtered)	10 0
Lanolin anhydrous	20 0
Zinc oxide	6 0
Talc	6 0
Petrolatum q s ad	60 0

Sig Apply locally

Uses This is an excellent preparation for infantile eczema

Crude Coal Tar Unguentum 2 per cent

℞ Crude coal tar	8 0
Pulv zinc oxide	8 0
Corn starch	60 0
Petrolatum	60 0

Sig Apply twice daily locally and cleanse with *olive oil*

Directions Mix the first two ingredients and the last two separately then work them together thoroughly The color should be greenblack or grey If green or if fine globules settle out the preparation is worthless See comments on crude coal tar therapy page 000 An excellent preparation is that made under Prof White s directions by the Eastern Drug Co at Boston Mass Too close bandaging results in an out cropping of pustules The tar can best be removed by warm liquid petrolatum and from 8 to 16 ounces should be included in each prescription to the patient for this purpose

Covermark This preparation is made by Lydia O'Leary, 551 5th Avenue, N Y C

Ethyl Aminobenzoate Ointment (Benzocaine Ointment)

℞ Ethyl Aminobenzoate	1 5
Benzyl alcohol	2 5
Menthol	0 06
Liq phenol	0 3
Anhydrous lanolin	6 0
White petolatum q s ad	30 0

Sig Apply as an ointment to abraded or denuded areas of skin

Phenol Ointment U S P (Carbolated vaseline)

℞ Phenol	2 0
Yellow wax	5 0
Petrolatum q s ad	100 0

Sig Used as an ointment—antipruritic and mild dermal anodyne

Chloroform Liniment with Methyl Salicylate

℞ Spirit of Camphor	20 0
Chloroform	30 0
Turpentine	10 0
Methyl salicylate	30 0
Camphor and soap liniment q s	180 0

Sig Used as an active local anodyne and *rubefacient* Apply with inunction

Dandruff Lotion

Resorcinol 2% alcoholic solution
Castor oil 1%

Dusting Powder The following preparations can be used in the management of hyperidrosis or *trichophytosis*

#1 ℞ Alum 3 0
Na Hyposulfite 12 0
Boric acid
Mg Carbonate aa q s ad 60 0

#2 ℞ Na thiosulfate 6 0
Boric acid 30 0

Sig Dusting powder to be used several times weekly

Fowler's Solution (Liq potassii arsenitis) Dose Minims 1 to 3 three times daily

Note Asiatic pills are better as they are less prone to produce arsenical keratoses and pigmentation

Gentian Violet

℞ Gentian violet	3 0
Alcohol 80%	12 0
Dist water	60 0

Sig Paint locally twice daily

K Lotion for Poison Ivy

℞ Phenol	0 2
Menthol	0 3
Glycerin	3 6
Kao-magma	120 0
Coloring—trace	

Sig Apply locally as a lotion

K and M Gum Astringent

℞ Tinct Kino	5 0
Tinct myrrh	10 0

Sig Paint on gums with cotton applicator twice daily diluted 1 teaspoon to a cup of water as mouth wash

Lassar s Paste

℞ Salicylic acid	1 3
Corn starch	8 0
Zn oxide pulv	8 0
Vas alba q s ad	30 0

Sig Daub on thickly or apply to dressings

Lotio Alba

℞ Potassii sulfurates	1 0
Zinci sulfatis	1 0
Aqua ad	120 0

Sig Apply locally to the face with a cotton sponge

Note Always prepare fresh in a clean bottle as the preparation is only efficient for two weeks It is desirable when a sulfur lotion milder than Vlemnick s is required

Oxyquinoline Ointment

℞ Oxyquinoline	0 60
Chloretone	1 20
Liq petrolatum	4 00
Scarlet red ung 5% q s ad	120 00

Uses To stimulate epithelial growth in ulcers

Potassium Permanganate Solution This is prescribed in various strengths from 1 8000 to 1 10 000 and is useful as a wet dressing especially when there is secondary infection and as a forerunner to aluminum subacetate in pyodermas and badly cared for eczemas The dressings should be kept wet and not allowed to dry It is well to instruct the patients how to dilute the solution and to show them the color of the diluted solution which resembles that of Burgundy wine

Face Powder without Orris Root This can be furnished by

E R Mansfield Co
1969 S Los Angeles Ave
Los Angeles Calif

Macauly Laboratories
P O Box #6
Flatbush Station
Brooklyn N Y

Potassium Iodide This is usually prescribed in a 1 1 solutions as follows

℞ Potassium iodide	30 0
Water	30 0

Sig Gtt in full glass of water with meals Increase as directed

In the treatment for blastomycosis the dose may reach from 200 to 300 grains three times daily A new product *Enkide* (Brewer) is an enteric coated tablet containing 15 grains of potassium iodide this is ideal in that it is well tolerated and can be accurately measured without the inconvenience of counting drops

Ruggles s Cream

Glycerite of starch	20 0
Zinc oxide	36
Quince seed	10
Hot water	1 8
Stearic acid	3 0
Sodium borate	03
Potassium carbonate	03
Water—add when reaction ceases	30 0

Sig Apply locally

Uses In dry eczema of the palms and in icthyosis

Schamberg's Lotion

Mentholis	0 6
Ac Phenolis	4 0
Olive Oil	120 0
Lime water	120 0
Pulv zn oxide	20 0

Sig Apply locally

Sulfur Bath

Precipitated sulfur	480 0
Na hyposulfite	120 0
Dil sulfuric acid	240 0
Dist water q s ad	4,096 0

Sig 1 pint to each bath

Sodium Thiosulfate Solution

Na thiosulfate crystals	120 0

Sig 5 heaping tablespoons to 1 pint of water makes a 20% solution

Ung Picis Liquidum

Picis liquid	0 6
Salicylic acid	0 6
Ung Zn oxide q s	30 0

Sig Rub in locally

Zinc Sulfur Paste

Sulfur	3 0
Resorcin	1 5
Kaolin	1 5
Ung zinc oxide	30 0

Sig Rub in well after washing the face with castile soap and hot water

Uses In severe acne, the coating gives cosmetic improvement and removes the superficial comedones Only a small amount should be used rubbed in well If the patient is under x ray treatments it should be used only in the intervals between treatments Any tendency to hypertrichosis should be watched

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Chapter XVIII

CHEMOTHERAPY THE CLINICAL USE OF THE SULFONAMIDE DRUGS

Chemical Considerations

The structure of the sulfonamides is essentially simple being based fundamentally upon the benzene ring When an amino ($-NH_2$) group is substituted for one of the hydrogens of the ring analine is formed when a sulfonyl ($-SO_2$ OH) group is substituted for another hydrogen of the benzene ring sulfanilic acid is obtained If the —OH group is then replaced by an —NH group the result is para aminobenzenesulfonamide or sulfanilamide With this as the starting point, one of the hydrogen atoms of the $-SO_2NH$ group may be replaced by any one of a number of radicals, and the resulting compounds have different antibacterial, toxic and physical characteristics

The bacteriostatic power of the sulfonamides is dependent upon many factors namely, the quality of the medium in which the organisms are growing the temperature the pH of the medium, the concentration of the organisms the resistance of the particular strain and the speed with which the liver acetylates the drug Acetylation is the term used to describe an important reaction occurring within the body which affects the therapeutic usefulness of the sulfonamides This process occurs chiefly in the liver and consists of the substitution of an acetyl ($-COCH_3$) group for one of the hydrogens of the amino group attached directly to the benzene ring The acetylated form generally appears therapeutically inactive in the body by itself

Mode of Action

The activity of the sulfonamide drugs depends upon an inhibition of the multiplication of virulent bacteria in the tissues This bacteriostatic activity can be nullified by para aminobenzoic acid meat and yeast extracts in vitro and pus necrotic tissue autolyzed bacteria and procain in vivo A belief widely accepted is that the sulfonamides act by competitive inhibition of an enzyme reaction (12) The bacteriostatic action of sulfonamides does not occur immediately, i e multiplication progresses for about six cell divisions with Escherichia coli before it ceases in the presence of adequate concentrations of sulfonamides (13) This fact tends to emphasize the necessity of early treatment and may be the reason why some cases of pneumonia and meningitis are fatal in spite of treatment by a sulfonamide derivative to which the organism is susceptible

Toxicity

The sulfonamides are potentially dangerous drugs the best now available giving rise to toxic reactions which are occasionally fatal This being true, it follows that it is wrong to give them without specific indications The common tendency of giving them for head colds and any condition associated with a febrile reaction is mentioned only to be condemned Many feel that by such indiscriminate use of the drug we are depriving the patient of possible future benefit when he may be in desperate need of same through his acquiring a drug sensitivity Before administering a sulfonamide drug inquiry should be made as to whether or not the patient had previously taken a similar drug, and whether any reactions occurred If a history of a previous reaction is obtained it is well to start treatment cautiously with another analogue of the drug

A summary of the reported reactions with respect to each drug will be found on the appended table LXV See page 1033

A large proportion of these reactions are due no doubt to the large doses necessary and the low solubility of their acetyl derivatives These properties combined with the high renal clearance of these compounds frequently lead to the precipitation of insoluble compounds in the renal tubules and pelvis as well as in the ureters With drugs of which the degree of ionization varies significantly in the pH range of the urine i e acetyl sulfadiazine the solu

bility can be greatly increased by rendering the urine alkaline. Crystals are rarely found in sulfanilimide treated cases but they occur in two thirds of patients receiving sulfathiazole or sulfapyridine, and in one twelfth of patients receiving sulfadiazine.

allowed to operate aircraft and special care should be observed in driving a car, crossing busy streets and operating machinery.

Acidosis occurs only with sulfanilimide and is readily diminished by giving bicarbonate of soda with it. *Cyanosis*, a common manifesta-

TABLE LXV

The Frequency of Toxic Reactions in Sulfonamide Therapy

Reactions	Sulfanilamide	Sulfapyridine	Sulfathiazole	Sulfadiazine	Sulfasuxidine	Sulfamerazine	Remarks and Suggested Treatment
Cyanosis	Common	Common	Uncommon	Rare	Not noted	Not noted	Sedation if necessary. Do not stop the drug
Dizziness	Common	Common	Uncommon	Rare	Not noted	Not noted	Sedation is all that is necessary
Nausea and Vomiting	Fairly common	Common	Common	Unusual	Rare	1.3% (400 cases)	Sedation will suffice in most cases
Headache	Common	Common	Uncommon	Rare	Not noted	Not noted	Mild sedation
Toxic Psychosis	0.6%	0.3%	Rare	Not noted	Not noted	1% (400 cases)	Stop drug and force fluids
Acid	Common	None	None	Rare	Not noted	Not reported	Give alkali by mouth
Agranulocytosis	0.1% commonest 12th day	0.3%	Rare	Rare	Rare	Rare	Stop drug and force fluids. Transfuse and give pentnucleotide and crude liver extract intramuscularly. As a rule transfusion is ineffectual and some think it may depress the bone marrow especially when repeated
Drug Fever	10% 5-9th day	3% 5-9th day	10% 5-7th day is common in sensitized people	1.5%	Not noted	1.5 to 2% between 5-14th day	Stop the drug
Dermatitis	[illegible]	2%	4%	2%	Not noted	2.3%	Stop the drug and force fluids
Hematuria	Not recorded	8%	2.5%	1%	Not noted	1.3%	Force fluid and give bicarbonates to bring blood bicarbonate level to normal. May have to catheterize and lavage the ureters with mild alkaline solutions to break up and dissolve any calculi or precipitates in ureters
Leucopenia	2%	2%	1.5%	1.5%	Not noted	2.0%	Stop drug and force fluids. [illegible] daily
Purpura	Reported	R[illegible]	Rare	Not reported	Not noted	Not reported	Stop drug and force fluids
Renal damage	Does not occur	8%	5-10%	5%	Not noted	Urinary complications reported and buffered alkalies will prevent or minimize them	Force fluid and alkalies

Nervous symptoms usually appear soon after therapy has been started. They are lassitude, anorexia, nausea, vomiting, and sometimes a frank psychosis. The nausea and vomiting are central in origin. Various vitamin preparations as well as oxygen have been advised for their control. The ambulatory patient taking the drug should be warned that his reaction time may be retarded. He should not be

tion of sulfanilimide therapy, is very slight or absent with the other drugs. *Blood disturbances* may assume any form. Low grade anemia is a common accompaniment of prolonged sulfonamide therapy. It may be relieved by transfusion. Agranulocytosis and granulocytopenia may occur with any of the drugs.

Manifold *skin disturbances* are seen, par

ticularly the erythematous, both morbiliform and nodose, as well as the occasional case of exfoliative dermatitis The rashes are often accompanied by arthralgia, splenomegaly fever and lymphadenopathy They most frequently occur from the 5th to the 15th day after beginning treatment Such patients will usually have a similar reaction on subsequent treatment, even though the dosage is small

Drug fever, with or without a rash may occur Longcope (14) has recently commented upon the similarity of this latter group to serum sickness pointing out that although these drug reactions have many characteristics of sensitization phenomena, antibodies have not been demonstrated and most workers have failed also to demonstrate skin reactions to the drugs with any regularity

Fluid Intake During Sulfonamide Therapy

Fluid intake does not need to be restricted in sulfonamide therapy The idea of restricting fluids in order to secure higher concentrations of the drug has been abandoned even in infections of the genitourinary tract (15) since it is now the belief that the drug acts mainly before it enters the lumen of the tubular tract (16) The urine output should be estimated every twenty four hours and it should not be allowed to fall below from 1200 to 1500 c c

Should Alkalies Be Given with the Sulfonamides?

With the exception of sulfapyridine a study of the solubility figures of the various sulfonamides reveals that they are more soluble at higher pH levels It has been conclusively shown that crystalluria and evidences of renal damage and obstruction are markedly decreased or absent when the urine is maintained neutral or alkaline during treatment Alkali therapy will not prevent sulfapyridine reactions however as it has been shown that both the free and combined sulfapyridine have about the same solubility at both pH 5 5 and pH 7 5 Acetylsulfathiazole is about four times more soluble in alkaline urine than in an acid urine Acetylsulfadiazine rises from 20 mg per cent solubility at pH 5 5 to 512 mg per cent at pH 7 5 In a similar manner sulfamerazine sulfamethazine and sulfapyrazine and their acetyl compounds are more soluble at higher pH levels

No routine dosage of alkali can be suggested to accompany the sulfonamide drugs, this can be best estimated by testing the urine for pH and giving sufficiently of alkalies to insure its being maintained at a neutral or alkaline reaction In some cases, 15 grams of sodium bicarbonate daily are necessary to produce the desired alkalinity

Incompatibilities

There are but few contraindications to the administration of other drugs with the sulfonamides The use of local anesthetics derived from para aminobenzoic acid should be avoided since this amino acid is liberated when the anesthetic breaks down and antagonizes the action of the sulfonamide Patients taking the drug should not be subjected to working in strong sunlight, nor should they be given ultra violet therapy The sodium salts of the sulfonamides should not be combined with parenteral fluids such as glucose or citrated blood since the alkalinity of the drug is frequently so marked that it causes changes in the fluid which render it unfit for either intravenous or subcutaneous administration

Characteristics of the Various Sulfonamide Derivatives

Comparing the drugs individually, characteristic points of difference stand out *Sulfanilimide* is conspicuous for the frequency of cyanosis acidosis, and acute hemolytic anemia though the author knows personally of one case a U S Coast Guardsman who by actual count admitted taking several thousand tablets without any serious results *Sulfapyridine* is characterized by its tendency to cause nausea and vomiting as well as its antipyretic action (1) (2) On account of this last feature the temperature alone is an extremely unreliable criterion for the control of the existing infection by this drug *Sulfathiazole* is very well tolerated but it is likely to sensitize and cause renal complications as well as to cause fever and a rash on subsequent administration It is difficult to maintain a desired blood level with this drug since it is excreted rapidly *Sulfathiazole and sulfadiazine* are very well tolerated by most

patients High blood levels are easily achieved with *sulfadiazine* because of its slow excretion which makes the administration of the drug however not entirely without danger since serious toxic reactions may occur after cessation of therapy Renal complications may follow sulfadiazine therapy in much the same way as with sulfathiazole or sulfapyridine In general, the toxicity of the latest sulfa drug *sulfamerazine* is low and is no greater than that of sulfadiazine Recent studies have shown it may cause urinary tract disturbances and most investigators now recommend that alkalies be administered with it

SULFAMERAZINE

Studies in laboratory animals have shown that sulfamerazine is more rapidly and completely absorbed from the gastrointestinal tract as well as more slowly excreted from the kidney than is *sulfadiazine* When a comparison of the blood concentrations is made there is little difference in their toxicities Studies in human subjects reveal a more rapid rise in concentration as well as a more sustained level of concentration on a smaller dosage than is possible with the other sulfonamide derivatives It appears that the concentrations of sulfamerazine in cerebrospinal pleural and ascitic fluids is comparable to that of sulfadiazine as well as the fact that smaller amounts are required to produce and sustain a desired blood level the likelihood of crystal and concretion formation is less with sulfamerazine than with sulfadiazine

The drug is given orally the initial dose being 3 grams followed by one gram every four six or eight hours depending upon the nature of the infection and the blood level until the temperature has remained normal for from forty-eight to seventy two hours It has been found that following an initial dose of 3 grams and 1 gram every four hours thereafter an average plasma concentration of 15 4 mg per 100 c c can be expected in those who receive 1 gram every six hours after the initial dose 12 7 mg per 100 c c and in those receiving 1 gram every eight hours after the initial dose the plasma concentration averages from 10 5 to 11 0 mg per 100 c c

It can be seen that with the rapid absorption obtained with this drug parenteral use may not be necessary, although it can be so given if the need is urgent The drug is especially recommended for pneumococcal and meningococcal infections Comparable results to those of sulfadiazine have been reported in the treatment of streptococcal infections of the urinary tract and gonococcal and staphylococcal infections *Sulfathiazole* is more effective than either *sulfamerazine* or *sulfadiazine* in the management of staphylococcal infections and it is still the drug of choice in the sulfonamide treatment of gonorrhea

SULFAGUANIDINE

The synthesis and physical properties of this drug were described by Robbin in 1940 From studies both in vitro and in vivo of its antibacterial activity it stands among the more potent sulfonamide compounds It has been suggested for use in the therapy of dysentery cholera typhoid and in the sterilization of the intestinal tract before operations on the bowel The experience with this drug has proved to be quite variable and leads to the belief that it is far from being safe It inhibits the growth of laboratory animals and even in those periods in which the rate of growth was normal the thyroid of the test animals showed hyperplasia hyperemia and hypertrophy (3) In some animals the thyroid gland increased in size from three to eight times This phenomenon results from the fact that certain organisms of the bowel play a part in the synthesis of essential nutrients it is believed that sulfaguanidine destroys this beneficent effect thus giving rise to a nutritional deficiency

Recent studies in the dysenteries reveal sulfadiazine sulfathiazole and even sulfasuxidine are more effective than sulfaguanidine

SULFASUXIDINE (SUCCINYL SULFATHIAZOLE)

This drug appears to be the best drug to use in eliminating organisms from the convalescent carriers of dysentery Its activity is confined to the intestinal tract and a bacterial specificity is shown for B Sonne Duval B Flexner and Shiga strains Coliform organisms Proteolytic anaerobic bacteria and clostridia A high concentration of the drug can be maintained in the human gastro intestinal tract though at the time due to low absorption only

extremely low concentrations occur in the blood, rarely exceeding 2 mg per 100 c c The strongly antibacterial action appears to be due to the sulfathiazole liberated in the bowel by *hydrolysis* In a study of the use of this drug in the treatment of dysentery carriers, the dysentery bacilli disappeared from the stools within one week after treatment had been started, and remained absent during a subsequent period of from 30 to 60 days An adequate fluid intake must be maintained while the drug is being taken

SULFATHALIDINE (PHTHALYLSULFATHIAZOLE)

Preliminary experimental studies of this drug have shown that it possesses several characteristics which point to its being more effective in certain respects than sulfasuxidine According to Poth (4) it is absorbed to a lesser degree than sulfasuxidine, it maintains a low concentration in the blood and is rapidly excreted in the urine It has from two to four times the bacteriostatic activity of sulfasuxidine in the bowel but it does not alter the consistency of the stools Micro organisms are greatly reduced within twenty four hours and coliform organisms are reduced to less than 1000 per gram of wet feces within three days after administration of the drug It appears to be effective in the presence of a persistent watery diarrhea

OTHER SULFONAMIDE DRUGS

Other sulfonamide compounds that have been reported on in the late literature are sulfapyrazine and *sulfamethazine They are* closely related chemically to sulfadiazine Experiments show they have about the same bacteriostatic effect upon the pneumococcus as does sulfadiazine, and the clinical reports indicate the curative power to be about equal that of sulfadiazine There are however marked pharmacological differences in these drugs Sulfapyrazine is slowly absorbed and excreted, and accordingly remains in the blood for a longer time than sulfamethazine or sulfamerazine Both sulfamethazine and sulfapyrazine show a high degree of acetylation with a decrease in the free and active portion thus making treatment on this basis ineffective in some instances, as well as causing serious toxic reactions to occur

Definite Indications for Sulfonamide Therapy

1 Infections due to susceptible organisms should be treated with the sulfonamides *only if they are severe or spreading* The effectiveness of therapy will always be limited by the accuracy of the bacteriological diagnosis

2 *Three day trial of therapy* When a patient is seriously ill with an infectious disease and a definite diagnosis cannot be made one should not withhold sulfonamide therapy since the mortality caused by the drug itself is not more than 0 2 per cent In a patient seriously ill this three day trial of therapy is justified Perhaps by the end of that period a definite bacteriological diagnosis may have been reached Should no response to the drug occur by the end of three days there is little to be gained by continuing it any further If the cause is in doubt and the patient very ill, *both penicillin and sulfonamides should be given* Since the influenza bacillus and Friedlander s bacillus are unaffected by penicillin therapy should consist of full dosage of sulfadiazine or sulfamerazine and the use of specific antiserum which is available for Friedlander s bacillus type A and B, and for influenza bacillus type B

3 *Meningitis* The sulfonamides are extremely effective in the therapy of *meningococcic meningitis* but penicillin should also be given to those who are severely ill and who have a skin rash The organisms of *pneumococcic* and *streptococcic meningitis* are likewise susceptible to both the sulfonamide drugs and penicillin therefore therapy consists in combined sulfa penicillin administration As pneumococcic meningitis has a tendency to relapse when treatment is stopped it should be continued for ten days after the spinal fluid cultures have been declared negative i e the sugar is normal and the cell count is below 100 with a predominance of lymphocytes *Staphylococcic meningitis* calls for combined sulfa penicillin treatment the penicillin to be given both intramuscularly and intrathecally

4 *Dysentery* Recent work has shown sulfadiazine to be the drug of choice in the therapy of dysentery Treatment should be continued for at least four days after stool cultures are negative for the infecting organisms

5 *Prophylactic Therapy* Prophylaxis car

ries a definite risk of sensitizing patients so that future sulfonamide therapy for more important reasons may produce severe reactions Definite indications are

a Dirty traumatic wounds
b Burns
c Influenza during epidemics when complicated
d Known exposure to gonorrhea
e Rheumatism or congenital heart disease for 24 hours before and 72 hours after tonsillectomy dental extraction or any operative procedure that might permit a subsequent bacteremia
f Contamination of peritoneal or pleural cavities

Mass Chemoprophylaxis

Early in 1943 following a relatively circumscribed incidence of measles in a Naval training center many serious types of respiratory infections occurred These were traced to a *hemolytic streptococcus which not only maintained* its pathogenicity but manifested an increased virulence It became highly communicable produced intense scarlet fever precipitated severe rheumatic attacks and became invasive The bacteria identified serologically as types 17 19 and 1 maintained their pathogenicity when transplanted to other sections of the country and even initiated streptococcal outbreaks at activities situated in the Southern states The seriousness of the situation was recognized early and was met with the institution of a long term streptococcal *control program*

This program has contributed the outstanding medical contribution of the year (17 18) and a brief summary follows

> An experimental population approximating 600 000 an equivocal environmental condition and controlled particulars that only military situations can afford validate the observations in this instance in a manner that will be difficult to duplicate in any experiment on living subjects

Its objectives were achieved by the use of prophylactic doses of sulfadiazine The *effectiveness of sulfadiazine prophylaxis* had been indicated in previous reports (19–22) but to test its mass applicability under controlled conditions and to determine a standard prophylactic dose, several activities seriously handicapped by a high incidence of respiratory infections were selected The administration of 1 gm daily to all hands was accompanied by a precipitous contraseasonal decline in streptococcal infections and was followed by a marked drop in the incidence of rheumatic fever

Since the advent of chemotherapy concepts regarding sulfonamides have had to undergo considerable modifications Administration of subclinical doses has been considered conducive to drug sensitization, *induction of severe irreversible drug reaction* and the development of drug fastness in bacteria, employment over a prolonged period exposed the patient to blood dyscrasias

These and other contentions were proved invalid during the course of this study Dangerous untoward reactions occurred only once in 10 000 individuals receiving the sulfadiazine prophylaxis and these consisted of an exfoliative dermatitis and granulocytopenia

Drug fastness was apparently not initiated by administration of the prophylactic dose despite the extended program of six months

Thus mass prophylaxis with sulfadiazine becomes established and brings with it less serious sequelae than the administration of such a drug had led one to anticipate Its *effectiveness not only was apparent in the* reduction of streptococcal invasion but materially influenced the incidence of meningococcal pneumococcal and gonococcal infections The lessened morbidity and the saving of man-days have tremendous economic implications are recommended a continued use of this mode of prophylaxis

Military necessity will dictate the continuation of sulfonamide prophylaxis There seems little justification as far as the civilian population is concerned for the wholesale and uncontrolled use of long continued sulfonamides *except on an experimental basis with a carefully* controlled study (23)

Questionable Indications

a The prevention of scarlet fever or hemolytic streptococcus syndromes in exposed individuals

b Inlying catheters in patients who are having constant bladder drainage
c Bronchiectasis (Norris)

Contraindications to Sulfonamide Therapy

The following diseases do not respond to the administration of the sulfonamide drugs

a Viral or atypical pneumonias
b Psittacosis
c Influenza, unless epidemic and not complicated by pneumonia
d Common cold
e Typhoid fever
f Typhus fever
g Rocky Mountain Spotted Fever
h Neurotropic virus infections
  1 Poliomyelitis
  2 Encephalitis
i Acute exanthemata in the absence of bacterial invasion
  1 Measles
  2 Chickenpox
  3 Smallpox
j Infectious mononucleosis
k Toxic manifestations of scarlet fever
l Puerperal infections due to anaerobic streptococci
m Urinary tract infections due to enterococci
n Diphtheria
o Tetanus
p Yellow fever
q Dengue fever
r Mumps
s Rabies
t Amebiasis
u Trichinosis
v Acute rheumatic fever
w Fungus infections except actinomycosis
x Rheumatoid arthritis
y Tularemia
z Brucellosis

Mild Illness or Localized Infection When fever is absent and the inflammatory process indolent the sulfonamides are not very effective especially against organisms like the hemolytic streptococci Thus attempts to treat a mild attack of acute tonsillitis with the drug usually fail Janeway (5) rarely uses sulfonamides unless the temperature exceeds 102°F except in cases of acute nephritis when *sulfanilamide* may be given Localized infection associated with pus is resistant to the sulfonamides because of the inhibiting action of the pus

Other Contraindications to the Sulfonamides

a Previous severe toxic reactions to sulfonamides
b Leucopenia

Choice of Sulfonamide Drug

The choice of drugs with dosages and remarks concerning their administration is covered in the accompanying table See page 1039

In general, sulfanilamide is the least potent of the sulfonamides except against Group A of the hemolytic streptococci It is ineffective in pneumonia and gives poor results in the treatment of gonorrhea If a patient has had a toxic reaction to one of the sulfonamides, one should use a different one and be on the alert for toxic reactions during a second course Sulfanilamide or sulfapyridine should never be used routinely because of its toxic symptoms and the discomfort caused to the patient *Sulfanilamide* is recommended in acute hemorrhagic nephritis because it rarely injures the kidney *Sulfamerazine* is probably the best drug in *meningococcal* or *pneumococcal* infections with sulfadiazine a close second choice For *staphylococcal* infections the best drug other than penicillin is *sulfathiazole* Sulfathiazole is also the most effective drug for the treatment of gonococcal infections and sulfadiazine for hemolytic streptococcal infections From the available evidence *sulfadiazine* should be used to begin the treatment of all acute dysenteries changing to *sulfasuxidine* after four days According to Gold (7) *sulfathiazole* and *sulfapyridine* are preferable in the treatment of anthrax Both *sulfadiazine* and *sulfathiazole* are effective against almost all organisms causing urinary tract infections (with the exception of the enterococcus) namely the *B pyocyaneous* and *B proteus* However some prefer sulfathiazole to sulfadiazine

DOSAGE AND ROUTE OF ADMINISTRATION

In general the initial dose should be large enough to raise the blood level to an effective concentration Doses are then given to maintain the optimum concentration by balancing the amount excreted daily by the kidneys

TABLE LXVI

Doses and Indications for the Sulfonamides

Type of Infection	Disease of Organism	Choice of Drug			Adult Dose		Remark
		First	Second	Third	Initial Dose	Subsequent Dosage	
P rpe l sep and l c l p w th pread l d g t e lw di f to s b t m ry p la c ll l t s l ry g t a heob h t s d st myel t	Beta hemolytic streptococci	S D	S N	S T	3 t 4 gm d pe ding pon th I se ty of tl i fe t	0 5 to 1 0 gm e e y f r h s day a d n ght	M tai pt mum blood nc t a tio In e er l f ct s c give p te lly Stop d g if n results 72 h s Heat e t immob l to d d l age may b eces ary Pe ic ll the dr g of ch e in b tere mi te myel t and puerperal seps s
	Staphyl occ a s	S T	S D		Sam abo e	½ i it l lose e ry 4 to 6 ho rs	
S pt o e th oat Acute b c t F E N T i f t s	Beta hemolytic streptococcus	S D	S N	S T	2 t 3 gm	0 5 to 1 0 gm e ery 4 ho rs d y d and n ght	H t st d ag a d hot irriga t o s may be import t Pe icill of alue cell l tis of the f ce mo th and e k
Ca b l s f le m pet go an l thy m	St phyl oc s	S T	S D		Powd d drug l lly o t m t	5 to 25% strength	Pen ll n the d g of ch ice
S l t Fe	*Beta hemolytic streptococci*	S D	S N		0 1 gm p r kilo body we ght	½ i it l lo e e ry 4 l rs 2 to 4 gm da ly in d d d do s in co v l cent p d	Use tise m in e io s ses
Ac te N pl t s	Beta hemolytic strepto cci	S N			2 to 4 grams d ly in d ided d s through t the feb le peri d		Keep rin y outp t at l ast 1500 cc G eq l am ts of bica bonate w th the s lfan l mide
P m —Ea ly Empy m	Pneumococc s	S M	S D	S T	S D m y g 3 to 6 gm F i st d may b g en int e ously S M g ve 3 gm t l dose it m y be g e int ly if the p t e t ery ll	½ of tial dose ry 4 hou s day and ght S M g e 1 gm e ery 4 6-8 hours d p di g upon e rity f infectio G e bica bo ate with S M	I tial i tra ous loading dose of alue n se e c ses to ure early adeq ate blood c e tr t on S r m m y be n ess y in ert in ca s (b late al eve e ca s or in the eld ly) Wh re empyem sulfa resist a t pneumonia p es nt e pe cillin
	Hemolytic streptococci	S D	S M	S N	4 to 6 gm depen I ng po the se er ity f the i fect	*0 5 to 1 0 gm e ery 4 hou s day and ight*	Mai t blood con trat o P cillin of dist ct val e he
	Staphyloc	S T	S D	S M	4 to 6 gm	½ i tial lo e e y f r to s x h rs	S me as abo e S M d sag men t ed der P eum ccus p eu mo ia P cill drug f chol e
	Fr dlä d Ba ll s	S D	S M	S T	4 to 6 gm	1 gm e ery 4 h u s Of l ttle al e in ch ic infe t o s	C mbi e ith specif c a tis rum ava l able for type A a d B

TABLE LXVI—*Continued*

Doses and Indications for the Sulfonamides

Type of Infection	Disease or Organism	Choice of Drug			Adult Dose		Remarks
		First	Second	Third	Initial Dose	Subsequent Dosage	
Meningitis	Pneumococcus	S D	S M	S T	4 to 6 gm Can give intravenously to insure quick elevation of blood concentration (S M 3 gm)	½ initial dose of S D & S T every 4 hours day and night S M given 1 gm q 4-6-8 hours depending upon severity of illness	Continue treatment 2 weeks after clinical recovery [illegible] which the spinal fluid [illegible] valuable indicator Penicillin the drug of choice
	H Streptococci	S D	S M	S P	Same as above	0 5-1 0 gm every 4 hours a day and night	Penicillin [illegible] should be used when available
	Meningococcus †	S D	S M	S T	5 gm intravenously and 4 gm oral combination (S D or S T) S M given 3 gm intravenously in 5% solution Can give 3 gm orally	1 0 to 1 5 gm q 4 hours In fulminating cases may require intravenous antiserum When S M used give 1 gm q 4-6-8 hours depending upon severity	Determine drug levels on spinal fluid when possible Condition of spinal fluid will indicate cessation of chemotherapy Penicillin should be used for all infections not responding to sulfonamides
	H influenzae	S D	S P	S N	2 to 4 gm	1 gm every 4 hours Results poor	Rabbit antiserum available
	Staph aureus‡	S T	S D	S P	4 to 6 gm	½ initial dose every 4 hours	Maintain level of drug and continue therapy 2 to 3 weeks after clinical recovery Penicillin of use if available
Septicemia and Peritonitis §	Most organisms	S D	S M		3 to 6 gm	Same as above	May need transfusion of specific antiserum
	Staph aureus	S T	S M	S D	3 to 6 gm	Same as above	May need to drain abscesses
	Gonococcus septicemia or arthritis	S T	S D	S P	3 to 6 gm	0 5 to 1 0 gm every 4 hours	Artificial fever or penicillin needed in drug resistant cases
	E coli	S T	S D	S N	2 to 4 gm	0 5 to 1 0 gm every 4 hours	Some apply drug directly into peritoneum
Venereal Infections	Gonococcus	S T	S D	S P	1 gm q 4 hours six times daily	6 gm daily in divided doses for 5 days If results shown cut to q i d for period of 6th to 10th day	Penicillin the drug of choice Repeat Wassermann to rule out syphilis
	Lymphogranuloma venereum	S N	S T	S D	1 3 gm	1 gm three times daily	May need to continue for long period
	Chancroid Ducrey bacillus	S D	S T	S N	Local treatment with powder		Hot permanganate soaks are of value Rule out a concomitant syphilis

* Best results from combined sulfadiazine and penicillin therapy

† Sulfadiazine and penicillin equally effect[illegible] When penicillin used give intramuscularly in usual dosage as well as intrathecally 10,000 units daily Combined therapy indicated in fulminating type

‡ Requires two to three times the dosage of penicillin usually given

§ Penicillin the drug of choice in peritonitis due to gonococcus, pneumococcus, staphylococcus [illegible] hemolyticus

TABLE LXVI—*Concluded*

Doses and Indications for the Sulfonamides

Type of Infection	Disease Organism	Choice of Drug			Adult Dose		Remarks
		First	Second	Third	Initial Dose	Subsequent Dosage	
Urinary Infections—Pyelitis, Cystitis and Pyelonephritis	All organisms except Enterococcus	S D	S T		2 to 4 gm daily in divided doses. Drug more effective in alkaline urine; also give bicarbonate	In mild infections 1 gm t.i.d. is sufficient	Many require surgery for stones. Repeated blood levels desirable as in presence of depressed renal function the rate of drug excretion is decreased
Lobar Pneumonia—Atypical Pneumonia—Endocarditis—Pericarditis, Peritonitis and Laryngotracheobronchitis	Pneumococcus	S M	S D	S T	3 to 6 gm. Can give initial dose intravenously. If S M used total dose 3 gm	½ of initial dose q. 4 to six hours. In serious cases use type specific serum. Give 1 gm q. 4-6-8 hours depending upon severity of the infection	Where S M used give bicarbonate and keep urine pH at 7.5 for best results. Penicillin the drug of choice
Actinomycosis	Actinomyces	S D	S N		4 gm daily for many months in divided doses. Of limited value. Beware of toxic effects		Penicillin the drug of choice
Trachoma	Virus	S P	S N		1 to 3 gm	1 gm t.i.d.	Local treatment needed also
Undulant Fever	Brucella	S T	S N		1 to 3 gm	1 gm q.i.d. for 2 or 3 weeks. Of some value in the acute attacks	
Anthrax	B. anthracis	S T	S P		3 gm	1.0-1.5 gm q. 4 to 6 hours	Antiserum of value. Penicillin the drug of choice
Gas Gangrene	Cl. welchii	S D	S T	S N	3 to 6 gm orally plus local implantation	1 gm every 4 hours day and night	Zinc peroxide locally. Roentgen therapy of great value as is antitoxin. *Penicillin the drug of choice*
Otitis Media	H. Influenzae	S D	S P	S N	1-3 gm	0.5 gm every 4 hours	
Bacterial Endocarditis	Strept. viridans Gonococci	S T S D	S D S T		4 grams 4 grams	*1.5 grams every four hours.* Same as above	Penicillin is the best agent available today. See pages 275-276
Bacillary Dysentery	B. dysenteriae	S D S S S G	S S	S G	6 grams in acute dysentery but to *start with S D for 4 days then switch* to S S. Dosage after initial dose for S D is 1 gm q.i.d. If S S is used alone see next column for dosage	3.5 gm every 4 hours until amount of stools below four daily then cut dosage to every 8 hours or three times daily until the stools are normal for four days when drug can be stopped	While the patient is on sulfasuxidine give no mineral oil. Control watery diarrhea before giving the drug. No bicarbonate is needed

S M Sulfamerazine
S D Sulfadiazine
S T Sulfathiazol
S P Sulfapyridine
S N Sulfanilimide
S S Sulfasuxid
S G *Sulfaguanidine*

Since the clearance rate of the kidney depends upon its functional capacity, the patient should be questioned about any previous episode of nephritis, nocturia, etc, and a complete urinalysis should be made The commonest error is to give too small a dose, which is worse than no treatment at all, for at best only a partial suppression of the infection is accomplished and the patient has a chance of developing some degree of sulfonamide resistance It has been shown that in such cases when the disease has been contracted by others, they too have developed resistance to sulfonamide therapy

Therefore, when it has been decided to give the sulfonamides, they should be administered in adequate dosage in order to bring the infection under control as soon as possible With the wide publicity given the sulfonamide drugs, the general practitioner may often be confronted with anxious relatives who are desirous of knowing why the patient is not receiving one of the 'sulfa' drugs They may even "demand" that he receive it With all the facts in mind and realizing that in the case in question chemotherapy will be useless, and may be ill advised and cause complications the physician should have enough courage to withhold the drug and not fall into the error of thinking 'It can't do any harm and it may do some good

Intravenous Use of Sulfonamides *Sodium sulfadiazine* has great advantages over sodium *sulfathiazole* or *sulfapyridine* in that it is excreted much more slowly, and therefore a patient may be given a large initial loading' dose followed by intravenous injections of 2 grams every eight to twelve hours to maintain an effective blood concentration It is difficult to maintain a satisfactory blood level using *sodium sulfathiazole* and *sulfapyridine* since these drugs are rapidly excreted and repeated doses by the intravenous route are dangerous When sulfamerazine is used in severe infections 3 grams in distilled water intravenously, are recommended as the initial dose Oral medication will maintain a satisfactory blood concentration thereafter

Subcutaneous Use Either 0 5 per cent solutions of *sodium sulfadiazine sulfathiazole* or *sulfapyridine* in normal saline may be used subcutaneously *Sulfanilamide* in 0 8 per cent saline solution may also be used It has been found that *sodium sulfadiazine* may be given in concentrations as high as two per cent subcutaneously without ill effects

For a patient who is severely ill, nauseated and distended, an intravenous "loading' dose is recommended, since an adequate blood level is thereby immediately established and several hours are saved during which time the infection may be brought under control A sufficient number of patients absorb these drugs poorly or irregularly when they are given orally to make it somewhat risky to start therapy by the oral route in a very sick patient

Enough is known now about these drugs to make frequent blood concentrations superfluous and in most cases only of academic interest The blood level should be determined when a patient does not respond to therapy in from twenty four to thirty six hours, when an abnormality of the urinary tract prevents measuring the urinary output or when parenteral therapy or administration through a stomach tube must be used

Topical Use of the Sulfonamides Recently, numerous preparations containing sulfonamide derivatives have become available and their use has been indiscriminately advocated for the local treatment of minor skin and mucous membrane lesions Needless to say the indiscriminate use of these preparations is to be deplored because of very definite potential hazards involved in their use

The topical application of such compounds is generally effective against *chancroid ecthyma* and superficial primary *pyogenic infections* such as *impetigo* They are of slight or questionable benefit in pyodermas complicating inflammatory eruptions and are of no value in other skin diseases

A dermatitis is the principal reaction which may occur as a result of the external use of a sulfonamide compound At first it is not unlike an ordinary contact dermatitis and it may be characterized by a vesicular bullous erythematous or papular eruption later becoming moist crusted and scaly If the topical application is continued the eruption may become generalized, it is most frequently eczematous in type although urticarial scarlatiniform morbilliform erythema multiforme like and pemphigus like reactions have been reported

Since reports indicate that reactions from the topical application of the sulfonamide drugs are increasing the indiscriminate use of these preparations should be restricted and their topical application limited to chancroidal and primary pyogenic infections of the skin The duration of their application should likewise be limited to five days as sensitization reactions may occur if such applications are continued beyond this time

TABLE LXVII

General Dose Schedule of the Sulfonamide Drugs with Effective Concentration

Route	Drug Used	Effective Concentration	Initial Dose of Drug	Maintenance Dosage	Remarks
Oral	Sulfanilamide	10–15 mg per 100 cc	4 gm orally	1.0–1.5 gm every 4 hours	Give equal amounts of Na bicarbonate Keep urinary output 1500 cc Use the drug as little as possible because of its toxicity
	Sulfapyridine Sulfathiazole Sulfadiazine	5–10 mg per 100 cc 4–7 mg per 100 cc 8–15 mg per 100 cc	4 gm orally 4 gm orally 4–6 gm orally	1 gm every four hours 1 gm every four hours 1.5 gm four times daily	Force fluids keeping urinary output at least 2000 cc daily Use sulfapyridine as little as possible and d t b m led by its t py t c effect
	Sulfam ne	10–15 mg per 100 cc	3 gm orally	1 gm every 4–6–8 hours depending upon the severity of the infection	Maintain output of at least 2000 cc and for best effect give Na bicarbonate with drug
Combined Oral and parenteral		Same as above	5 gm loading dose by intrave o t f sulfathiazole d a e G them the Na salt with 5% solution distilled water G sulfanilamide as 1% sol s l e G 3 gm of sulfamerazine n 5% sol in distilled water	Same as above	As mentioned before there is little use of sulfanilamide or sulfapyridine
Parenteral	Sulfanilamide	Same as above	5 gm intravenously	3 gm 1% solution three times daily intravenously or subcutaneously	
	Sulfathiazole Sulfadiazine	Same as above Same as above	5 gm intravenously 5 gm intravenously	2 gm four times daily as 0.8 to 5.0% solution 2 gm three times daily as 0.8 to 5.0% solution	
	Sulfamerazine	Same as above	3 gm intravenously	Oral maintenance dose with 1 gm every 4–6–8 hours depending upon the severity of the infection	For best results give Na bicarbonate and keep the pH of the urine at 7.5

Duration of Chemotherapy

It is difficult to lay down any rules or make any categorical statements regarding this problem There are no "routines" that can be advised, each case must be judged by itself In general it may be said that chemotherapy should be continued for at least 48 hours after all evidence of infection has disappeared In cases of pyogenic infection, it should be persisted in until all evidence points to localization and adequate drainage having been established In certain cases, it is given until sufficient antibodies have either been given or developed to maintain a cure In cases of deep infection it is difficult or impossible to know whether it has been brought under control a roentgen study and the sedimentation rate

Since the clearance rate of the kidney depends upon its functional capacity, the patient should be questioned about any previous episode of nephritis, nocturia, etc, and a complete urinalysis should be made The commonest error is to give too small a dose, which is worse than no treatment at all, for at best only a partial suppression of the infection is accomplished and the patient has a chance of developing some degree of sulfonamide resistance It has been shown that in such cases when the disease has been contracted by others, they too have *developed resistance to sulfonamide therapy*

Therefore, when it has been decided to give the sulfonamides, they should be administered in adequate dosage in order to bring the infection under control as soon as possible With the wide publicity given the sulfonamide drugs the general practitioner may often be confronted with anxious relatives who are desirous of knowing why the patient is not receiving one of the "sulfa" drugs They may even "demand" that he receive it With all the facts in mind and realizing that in the case in question chemotherapy will be useless, and may be ill advised and cause complications the physician should have enough courage to withhold the drug and not fall into the error of thinking "It can t do any harm and it may do some good"

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and the Escherichia coli This drug fastness may develop as early as three days after treatment has been started and it may last a year or longer Rogers and Fleming have suggested that sulfonamide treatment should be carried out very vigorously, and with large doses, in order to insure rapid destruction of the organisms in the hope of avoiding the development of drug fastness by sub lethal doses It cannot be denied that the dissemination of strains of organisms which have acquired a fastness to the sulfonamide drugs carries implications of vast importance to the public health

Bio Chemotherapeutic Agents

There have been recent developments in a new field of chemotherapy The products are named *tyrothricin tyrocidine gramicidin, streptomycin streptothricin* and *penicillin* The living cell is a store house of specific catalysts which are capable of performing almost every type of biochemical reaction This fact is involved in the phenomenon of antibiosis' which is the unfavorable effect of the life process of one cell species on those of another living in the same environment Studies have shown the presence of a soluble enzyme in certain sporulating soil bacilli which is capable of decomposing the specific polysaccharid of Type III pneumococcus in vitro Its mechanism is the removal of the capsular armor of the cell which is then susceptible to phagocytosis Soon microorganisms were found which would attack the living cell of the unrelated species and the chemical principles were isolated which were capable of bacteriostatic or bactericidal action (10)

TYROTHRICIN

This is an alcohol soluble and water insoluble fraction obtained from a culture of certain aerobic sporulating bacilli living in the soil In vitro it has strong bactericidal properties for many Gram positive and Gram negative organisms It is not a pure substance and from it have been separated tyrocidine and gramicidin

TYROCIDINE

This is anti bacterial for both Gram positive and Gram negative organisms It is a general protoplasmic poison it destroys the metabolic activity of the bacterial cell and ultimately causes complete lysis It is ineffective in vivo although some protective action has been obtained against a pneumococcus infection in the mouse

GRAMICIDIN

This compound does not act like tyrocidine It does not interfere with the oxygen uptake of the cell, nor does it destroy its structure It is a bacteriostatic agent It loses very little of its activity in the presence of animal tissues like serum or peptones It is highly effective against streptococci pneumococci staphylococci, diphtheria bacilli and other Gram positive organisms Meningococci and gonococci though Gram negative are somewhat susceptible to gramicidin Gramicidin is entirely without effect when administered intravenously intramuscularly, or subcutaneously but is highly effective when applied locally It has been used clinically in patients with skin ulcers and infections mastoids empyema osteomyelitis The application of 10 milligrams to a staphylococcus ulcer of the leg has resulted in complete sterilization of the area and sign of healing in twenty four hours Its use is limited however and it is of little use in mixed infections as the presence of Gram negative organisms exerts an inhibiting effect upon it

STREPTOMYCIN AND STREPTOTHRICIN

In the search for an effective agent against infections due to Gram negative organisms Waksman and Woodruff isolated a substance called streptothricin, derived from *Actinomyces lavendulae* More recently, Schatz Bugie and Waksman isolated a second antibiotic substance called streptomycin from *Actinomyces griseus*

Both of these substances are characterized by selective bacteriostatic activity against both Gram negative and Gram positive bacteria *Streptomycin* has much greater activity against certain specific Gram negative and Gram positive bacteria than does *streptothricin* For example Bacillus mycoides Serratia marcescens and the human strain of Mycobacterium tuberculosis are sensitive to streptomycin and fairly resistant to streptothricin whereas Staphylococcus aureus

may be of aid, therapy should be continued for about two weeks after apparent cure In *meningitis the temperature curve is a poor* guide when considering whether to continue or discontinue chemotherapy as many who recover run a febrile course for weeks after recovery has really occurred For this reason, the spinal fluid findings offer the best index of the clinical status of the patient and are considered to be the most reliable When all the polymorphonuclear leucocytes have disappeared from the spinal fluid, it is probable that the infection has been overcome The dosage *is then reduced for several days and if no* recurrences appear the drug is discontinued In chronic infections the drug may have to be continued for weeks and even months even though the patient may seem well When the drug is given for long periods it must again be emphasized that a sufficient urine output must be maintained if serious complications are to be avoided

Measures to Adopt When There Is No Therapeutic Response

In cases remaining febrile after at least two days of adequate chemotherapy

1 The diagnosis, particularly, in respect to the bacteriology should be re examined
2 It is probable that the blood level may be inadequate When this is impossible to confirm the maintenance dose should be increased or better an intravenous supplementary dose of 2 or 3 grams of sodium sulfadiazine should be given
3 Pus which inhibits the action of the sulfonamides should be suspected
4 Drug Fever The best criteria of drug fever are the absence of other possible causes of fever and its appearance five to fourteen days after the start of chemotherapy If a rash appears, the correct cause of the fever is apparent In the absence of skin manifestations there are no definite criteria which aid one in the recognition of the condition A fall in temperature will follow cessation of therapy if drug fever is present It is rapid in those receiving sulfathiazole and delayed in those receiving sulfadiazine or sulfamerazine
5 The organism may be a *sulfonamide resistant strain* As a rule poor results follow the administration of larger doses or a different sulfa derivative Penicillin *should be given if the organism is sus*ceptible to the drug
6 Complications such as endocarditis, osteomyelitis, empyema or abscess may cause a continued fever and leucocytosis in spite of intensive therapy Congenital defects or renal infections associated with stone also respond poorly to therapy

Recommended Chemotherapeutic Routine

1 One should inquire about previous chemotherapy and the occurrence of any reactions
2 The renal function should be investigated
3 If a blood culture is required, it should be obtained before chemotherapy has been started
4 When possible, a hemoglobin determination and a white cell count should be made before starting therapy
5 The patient should be told the name of the drug he is receiving and the importance of regular dosage and cautioned against the indiscriminate use of any left over sulfonamide drugs from home medicine cabinets if any similar symptoms develop at a later date
6 The importance of taking sufficient quan*tities of fluids should be stressed and the* output rather than the intake checked
7 Aviators who are taking the drug should be grounded for the duration of their treatment Those who drive cars or who work around machinery should be warned of accidents arising from anoxia and a slow reaction time
8 One should watch for toxic reactions and it should be remembered that it is possible to develop these reactions several days after the drug has been withdrawn

Drug Fastness

In the past year the problem of drug fastness in relation to the sulfonamides has received increasing attention Resistance to the sulfonamides seems to be a characteristic of certain strains of organism It is an established fact that some strains are able to acquire resistance if exposed to sub lethal doses of the sulfonamides This has been demonstrated for the gonococcus pneumococcus staphylococcus

and the Escherichia coli This drug fastness may develop as early as three days after treatment has been started and it may last a year or longer Rogers and Fleming have suggested that sulfonamide treatment should be carried out very vigorously and with large doses, in order to insure rapid destruction of the organisms in the hope of avoiding the development of drug fastness by sub lethal doses It cannot be denied that the dissemination of strains of organisms which have acquired a fastness to the sulfonamide drugs carries implications of vast importance to the public health

Bio Chemotherapeutic Agents

There have been recent developments in a new field of chemotherapy The products are named *tyrothricin tyrocidine gramicidin, streptomycin streptothricin* and *penicillin* The living cell is a store house of specific catalysts which are capable of performing almost every type of biochemical reaction This fact is involved in the phenomenon of 'antibiosis which is the unfavorable effect of the life process of one cell species on those of another living in the same environment Studies have shown the presence of a soluble enzyme in certain sporulating soil bacilli which is capable of decomposing the specific polysaccharid of Type III pneumococcus in vitro Its mechanism is the removal of the capsular armor of the cell which is then susceptible to phagocytosis Soon microorganisms were found which would attack the living cell of the unrelated species and the chemical principles were isolated which were capable of bacteriostatic or bactericidal action (10)

TYROTHRICIN

This is an alcohol soluble and water insoluble fraction obtained from a culture of certain aerobic sporulating bacilli living in the soil In vitro it has strong bactericidal properties for many Gram positive and Gram negative organisms It is not a pure substance and from it have been separated tyrocidine and gramicidin

TYROCIDINE

This is anti bacterial for both Gram positive and Gram negative organisms It is a general protoplasmic poison it destroys the metabolic activity of the bacterial cell and ultimately causes complete lysis It is ineffective in vivo although some protective action has been obtained against a pneumococcus infection in the mouse

GRAMICIDIN

This compound does not act like tyrocidine It does not interfere with the oxygen uptake of the cell nor does it destroy its structure It is a bacteriostatic agent It loses very little of its activity in the presence of animal tissue like serum or peptones It is highly effective against streptococci pneumococci staphylococci, diphtheria bacilli and other Gram positive organisms Meningococci and gonococci, though Gram negative, are somewhat susceptible to gramicidin Gramicidin is entirely without effect when administered intravenously intramuscularly or subcutaneously but is highly effective when applied locally It has been used clinically in patients with skin ulcers and infections, mastoids empyema osteomyelitis The application of 10 milligrams to a staphylococcus ulcer of the leg has resulted in complete sterilization of the area and signs of healing in twenty four hours Its use is limited however and it is of little use in mixed infections as the presence of Gram negative organisms exerts an inhibiting effect upon it

STREPTOMYCIN AND STREPTOTHRICIN

In the search for an effective agent against infections due to Gram negative organisms Waksman and Woodruff isolated a substance called streptothricin derived from *Actinomyces lavendulae* More recently, Schatz Bugie and Waksman isolated a second antibiotic substance called streptomycin from *Actinomyces griseus*

Both of these substances are characterized by selective bacteriostatic activity against both Gram negative and Gram positive bacteria *Streptomycin* has much greater activity against certain specific Gram negative and Gram positive bacteria than does *streptothricin* For example Bacillus mycoides Serratia marcescens and the human strain of Mycobacterium tuberculosis are sensitive to streptomycin and fairly resistant to streptothricin whereas Staphylococcus aureus,

may be of aid, therapy should be continued for about two weeks after apparent cure In meningitis the temperature curve is a poor guide when considering whether to continue or discontinue chemotherapy, as many who re cover run a febrile course for weeks after recovery has really occurred For this reason, the spinal fluid findings offer the best index of the clinical status of the patient and are con sidered to be the most reliable When all the polymorphonuclear leucocytes have disap peared from the spinal fluid, it is probable that the infection has been overcome The dosage is then reduced for several days, and if no recurrences appear, the drug is discontinued In chronic infections the drug may have to be continued for weeks and even months even though the patient may seem well When the drug is given for long periods, it must again be emphasized that a sufficient urine output must be maintained if serious complications are to be avoided

Measures to Adopt When There Is No Therapeutic Response

In cases remaining febrile after at least two days of adequate chemotherapy

1 The diagnosis particularly in respect to the bacteriology should be re examined
2 It is probable that the blood level may be inadequate When this is impossible to confirm, the maintenance dose should be increased, or better an intravenous sup plementary dose of 2 or 3 grams of sodium sulfadiazine should be given
3 Pus, which inhibits the action of the sulfonamides should be suspected
4 Drug Fever The best criteria of drug fever are the absence of other possible causes of fever and its appearance five to fourteen days after the start of chemo therapy If a rash appears the correct cause of the fever is apparent In the absence of skin manifestations there are no definite criteria which aid one in the recognition of the condition A fall in temperature will follow cessation of ther apy if drug fever is present It is rapid in those receiving sulfathiazole and de layed in those receiving sulfadiazine or sulfamerazine
5 The organism may be a *sulfonamide re sistant strain* As a rule poor results fol low the administration of larger doses or a different sulfa derivative Penicillin should be given if the organism is sus ceptible to the drug
6 Complications such as endocarditis os teomyelitis empyema or abscess may cause a continued fever and leucocytosis in spite of intensive therapy Congeni tal defects or renal infections associated with stone also respond poorly to therapy

Recommended Chemotherapeutic Routine

1 One should inquire about previous chemo therapy and the occurrence of any reac tions
2 The renal function should be investigated
3 If a blood culture is required, it should be obtained before chemotherapy has been started
4 When possible a hemoglobin determina tion and a white cell count should be made before starting therapy
5 The patient should be told the name of the drug he is receiving and the impor tance of regular dosage and cautioned against the indiscriminate use of any left over sulfonamide drugs from home medi cine cabinets if any similar symptoms develop at a later date
6 The importance of taking sufficient quan tities of fluids should be stressed and the output rather than the intake checked
7 Aviators who are taking the drug should be grounded for the duration of their treatment Those who drive cars or who work around machinery should be warned of accidents arising from anoxia and a slow reaction time
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(British penicillin 2) while the product of superficial culture extracted by chloroform is penicillin X (penicillin 3 or allopenicillin) Two other penicillin fractions have been identified penicillin IV and V It is quite possible that there are others, as yet undiscovered (28) (29)

Specificity of fractions Evidence suggests that each fraction has therapeutic specificity It is certain that the G fraction is less active against the gonococcus than crude penicillin, whereas penicillin X is more active than either

The amount of any one factor present in the marketed ampoule is not indicated on the label and fractional assay has not been considered practical to date

Penicillin G or 2 is the penicillin which is predominant in most available preparations and the term 'penicillin' practically connotes penicillin G The International Conference of Penicillin has recommended that an international penicillin standard be prepared from crystalline sodium penicillin G and that the international unit of penicillin be defined as the specific penicillin activity contained in 0 6 micrograms of the international penicillin standard (30) The international unit so defined is approximately equivalent to the Oxford unit which has been described as (1) the amount of penicillin which, when dissolved in 50 c c of meat extract broth will speedily inhibit the growth of a test strain of Staphylococcus aureus and (2) the amount of penicillin which, when dissolved in 1 c c of water, produces the same inhibition of the test strain of Staphylococcus aureus as does the arbitrary standard material supplied by Oxford University The Oxford standard is 42 units per milligram the U S standard 100 units per milligram

The proportion of the individual constituent factors is not consistent and one lot of commercial penicillin may contain more penicillin G than another notwithstanding that the two lots were grown simultaneously from the same parent mold in different tanks or successively in the same tank Penicillin produced by different manufacturers will show further variables

It is thus easily seen why penicillin may succeed or fail in the treatment of comparable pathologic conditions in the hands of different workers Likewise, it cannot be said that the effectiveness or ineffectiveness of any lot of penicillin now on the market is attributable to the presence or absence of any particular penicillin constituent These facts explain the variations observed in the British and American products and may account for the apparent contraindication regarding the efficacy of single-dose medication

There is some disagreement in the literature as to the mode of action of penicillin Fleming considered the action on bacteria to be lysis, it was believed that the organisms are inhibited and not destroyed—that the action was bacteriostatic and not bactericidal Most authorities are agreed on this While penicillin inhibits the growth and multiplication of bacteria the actual destruction and elimination of such organisms are no doubt effected by the normal defense mechanism of the host Contrary to an early report of Florey, it has now been shown by Bigger (31) that human serum does inhibit the action of penicillin *Escherichia coli* and other bacteria insensitive to penicillin produce a substance *penicillinase* which has the property of inactivating penicillin It can be prepared and its incorporation in culture mediums to inactivate penicillin present in the blood and exudates of those taking the drug has been suggested

Several methods for determining the concentrations of penicillin in the blood and body fluids have been described (43) but the information so gained does not seem to be of sufficient importance to warrant the routine determination of penicillin blood levels in clinical practice

The Clinical Use of Penicillin

Penicillin is furnished in both the sodium and the calcium salt and is so purified and dried that the final products have a potency of not less than 500 units per milligram They are sterile nontoxic and non pyrogenic and have a moisture content of not more than 2 5 per cent The drug may be stored for one year at −10 to −25 C without significant deterioration The sodium salt is furnished in ampoules and is diluted with pyrogen free water sterile isotonic sodium chloride solution or 5 per cent dextrose solution for clinical use The calcium salt likewise furnished in

Bacillus subtilis and Escherichia coli are sensitive alike to both substances Both substances are highly stabile and possess limited toxicity for animals Both drugs are active in vitro against a variety of bacteria, streptomycin being more effective against specific organisms, such as Pseudomonas aeruginosa and Proteus vulgaris

Absorption, Distribution and Excretion of Streptomycin

The blood level of streptomycin following a single intravenous injection, is better maintained than in the case of penicillin Detectable amounts of streptomycin have been found in the blood for six hours as compared with a period of from two to three hours during which penicillin may be detected even when the latter is injected intramuscularly

Following the injection of streptomycin the substance is distributed throughout most of the body fluids, including the blood urine ascitic fluid pleural fluid aqueous humor vitreous humor, amniotic fluid and bile Only small amounts of the drug appear in the cerebrospinal fluid of healthy individuals but according to Flippin the spinal fluid contained 25 units per c c in a single case of meningitis due to H influenzae The principal route of excretion after parenteral injection appears to be the urinary tract (24) (25) (26) (27)

Little transfer of streptomycin occurs between the blood and the lumen of the gastrointestinal tract in either direction Levels as high as 9 000 units per Gm have been found in the feces following oral administration Owing to the poor transfer of the drug across the wall of the alimentary tract it appears appropriate to use the drug both orally and parenterally in the treatment of infections in which the pathogenic organisms are found both in the gastrointestinal tract and in the blood stream Side reactions have not been alarming and no late toxic effects have been observed

Due to the greatly limited supply of streptomycin it is only being used in the following types of cases (1) seriously ill cord bladder patients with urinary *tract* infections due to Gram negative bacilli, (2) tularemia (3) Friedlander bacillus infections (4) meningitis due to Gram negative bacilli, and (5) bacteremia or septicemia due to Gram negative bacilli

Dosage Dosage of streptomycin is at present designated in S units One S unit is the amount which will inhibit the growth of E coli in 1 c c of broth The average daily dose recommended is 1 000 000 units per day given intramuscularly in the dosage of 250,000 units every six hours Cord bladder infections require from 3 to 5 days of treatment, other conditions require about 5 to 10 days treatment

The limited supply of the material and the equivocal results thus far obtained in the therapy with streptomycin of tuberculosis and typhoid fever do not justify its use for these conditions at present

PENICILLIN

Alexander Fleming reported the presence of a bacteriostatic substance in 1929 which he called penicillin At first he thought he was dealing with Penicillium rubium, but later he found it to be Penicillium notatum He applied the name penicillin to the filtrate containing the active principle of the culture This substance definitely inhibited the growth of many Gram positive organisms He predicted definite therapeutic possibilities for this agent and suggested that it might be an efficient agent when applied to or injected into an infected area In 1940 Chain, Florey and others prepared a highly concentrated and active preparation of penicillin suitable for clinical use It was not until 1942 however that the substance was extracted and obtained in crystalline form It was found to be an unstable acid with the probable formula of $C_{14}H_{19}NO_6$ or $C_{14}H_{17}NO_6—H_2O$ As its structure is unknown no synthesis has been possible That it is not a single pure chemical compound is apparent from the results of recent extraction and fractionation methods employed in its production

The fractionation of this substance into several components was brought about by crystallization of the products of the various methods of culturing *Penicillium notatum* Culture grown in flasks produces an active substance designated as penicillin F which is called penicillin 1 Culture grown in tanks the submerged culture produces penicillin G

therapy 30 000 to 50 000 units are advised daily and are given in two doses Each *dose may be dissolved in 1 000 c c* of normal sodium chloride solution or 5 per cent dextrose The first few hundred cubic centimeters are allowed to enter the vein rapidly whereupon the rate is adjusted to a flow of about 30 to 40 drops per minute

Intramuscular Injection Technique

1 The total volume of individual injections should be small from 10 000 to 50 000 units per c c of isotonic solution of sodium chloride

2 There are several methods available for intramuscular administration of penicillin It may be given in saline solution every three hours at longer intervals if the drug is incorporated into some substance that delays its absorption or it may also be given by a constant intramuscular drip 120 000 units in 250 c c

3 Delayed Absorption Methods of Administration When penicillin is injected intramuscularly (or intravenously) it is rapidly excreted in the urine and an effective therapeutic level in the blood stream is rarely maintained for as long as two hours following injection Methods for delaying the absorption of penicillin include (a) pro*longed chilling of the injected muscle site* for two hours before and from five to twelve hours after the injection, (b) the addition of epinephrine to the penicillin dose, and (c) combining the penicillin with a 6 per cent mixture of beeswax in highly refined peanut oil (44) (49) (45) Calcium penicillin must be used as the sodium salt is not suitable due to its hygroscopic qualities If available sesame oil is as good as if not better than peanut oil in the preparation of these mixtures

It has been found that following intramuscular injection of this material adequate concentrations of penicillin may be maintained in the blood for twelve hours or longer

Penicillin in Oil and Wax is packaged in *100 000 units per c c 200 000 units* per c c and 300 000 units per c c concentration The calcium penicillin used in the 300 000 unit per c c concentration has a potency of not less than 900 units per milligram and that in the other concentrations has a potency of not less than 750 units per milligram

All conditions require a minimum of 300 000 units per day Preparations containing 200 000 units per c c may be administered at twelve hour intervals If the quantity is 100 000 units per c c, administration at eight hour intervals is necessary Rotation of the site of injection is desirable the upper outer quadrant of the buttocks the anterior thighs and triceps are suggested sites **Do not use intravenously**

Topical Application Topical penicillin is calcium penicillin which conforms to the standards prescribed for that drug but it is a fine powder It may be packaged in vials or in foil enclosures containing not less than 10 000 units or not more than than 50 000 units of penicillin

For *postoperative mastoid infections* inject through a small inlying catheter directly into the cavity, 1 c c of a sterile solution containing 50 000 units once a day for a minimum of four days In *osteomyelitis* parenteral therapy may be supplemented by local instillation with 25 000 to 50 000 units in sterile solution two to three times daily In *empyema* after aspiration instill from 50 000 to 100 000 units into the cavity in a volume of solution less than the quantity of fluid aspirated In *superficial infections* of the skin caused by organisms susceptible to penicillin apply sterile dressings wet with a solution containing 1 000 units per c c one or more times daily as the condition indicates It may be advisable to supplement the local therapy with systemic medication

Penicillin Ointment Penicillin ointment is calcium penicillin in an ointment base Its potency is not less than 250 units per gram, and it contains not more than 50 viable microorganisms per gram It is packaged in collapsible tubes, *not larger than one ounce size* except the opthalmic ointment which is packaged in the one eighth ounce size

Penicillin Troches Penicillin troches are composed of sodium or calcium penicillin and may or may not contain masticatory substances The potency of each troche is not to be less than 500 units If the product contains masticatory substances the word chewing' or "masticatory shall appear with the name penicillin on the label

ampoules appears to have a greater stability than the sodium salt It is readily soluble and can easily be dissolved in physiologic saline solution or in 5 per cent glucose solution in distilled water It has been injected intramuscularly with no evidence of tissue irritation Penicillin is packaged in 100 000, 200 000, 500,000, 1,000,000 and 5 000,000 unit sizes

The benzyl ester of penicillin, as prepared by Cavallito, while not commercially available, shows great promise because of ease of preparation, enhanced stability, ready oral absorption and powerful chemotherapeutic action When taken orally, it is sufficiently potent to make it as effective as an equivalent weight of sodium penicillin given by subcutaneous injection

Routes of Administration There are three common methods of administering penicillin—*intravenous intramuscular* and *topical* The route of choice is intramuscular Subcutaneous injections are painful and the absorption of material so administered is erratic In meningitis, the drug is given through lumbar or cisternal puncture since the drug does not readily diffuse into the cerebrospinal structures following its systemic administration

A recent development is *oral penicillin* using various antacids buffers capsules and oils in an effort to protect the penicillin from the acidity of the stomach Clinical trials (September 1945) in cases of pneumonia gonorrhea and other miscellaneous infections have suggested that oral penicillin is feasible Three to five times as much penicillin is required when given by mouth as that required by intramuscular injection Obviously clinical judgement dictates that parenteral penicillin is the preferable route for initiating therapy in all severe infections and in those which experience has already shown to require prolonged treatment with large parenteral doses (32)

The intracolonic administration of penicillin is of no value being inactivated by bacterial enzymes present in the large intestine While antibacterial amounts of penicillin may reach the fluid in joints following intramuscular or intravenous administration it is frequently desirable to supplement systemic therapy by instillation of penicillin into the affected joints Herrell (33) advises instilling 10 000 to 20 000 Oxford units dissolved in 10 c c of isotonic saline solution into infected joints after aspiration has been performed The material is injected once daily for several days

Morgan (37) has shown that infusions of penicillin by way of the bone marrow are possible, as much as 46,000 units of penicillin being administered in nine hours by this route The sternum or clavicle can be used, and in children, the tibia or femur has been employed This method is to be used only when suitable veins are not available or, when as in the presence of extensive burns the intramuscular or intravenous method is not possible For technique, see page 1151

Barach and Vermilye Strieder, and Kay and Meade (38) (39) (40) (41) have stressed the apparent value of *aerosol penicillin* in the acute and chronic bacterial invasions and infections of the upper respiratory tract A highly concentrated penicillin solution can be nebulized and inhaled as a mist without diminishing its potency Knott and Clark (42) have demonstrated that penicillin dispersed as an aerosol in a room was fully active for ninety minutes

Method Of Preparing Penicillin For Treatment Penicillin may be dissolved in small amounts of sterile distilled pyrogen free water in sterile isotonic sodium chloride solution or in sterile 5 per cent dextrose solution When large unit ampoules are used in hospitals the contents of the ampoule should be dissolved in water or preferably saline solution so that the final concentration is 5 000 to 50 000 units per c c depending upon the circumstances of the case Solutions should be *stored under aseptic precautions in the ice box* and made up freshly every day Solutions for local or parenteral use may be diluted further depending on the concentration desired

Intravenous Injection Technique

1 The dry powder may be dissolved in sterile isotonic solution of sodium chloride in concentrations of 10 000 to 50 000 units per c c for direct injection through a syringe

2 The dry powder may be dissolved in sterile sodium chloride solution or 5 per cent glucose solution in lower dilution (25 to 50 units per c c) for constant intravenous

therapy 30 000 to 50 000 units are advised daily and are given in two doses Each dose may be dissolved in 1 000 c c of normal sodium chloride solution or 5 per cent dextrose The first few hundred cubic centimeters are allowed to enter the vein rapidly whereupon the rate is adjusted to a flow of about 30 to 40 drops per minute

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Penicillin Troches Penicillin troches are composed of sodium or calcium penicillin and may or may not contain masticatory substances The potency of each troche is not to be less than 500 units If the product contains masticatory substances the word 'chewing' or 'masticatory' shall appear with the name penicillin on the label

Penicillin Dental Cones Penicillin dental cones are composed of calcium penicillin but may also contain sulfonamides The potency of each cone is not less than 500 units, and the content of viable micro-organisms is not more than 50 per gram If a sulfonamide is present in the cone its quantity is not less than 0 032 Gm per cone

Precaution If sensitization occurs from the use of the topical products, discontinue their use immediately

Oral Penicillin Products At present the oral products are (1) Tablets or capsules buffered penicillin, (2) Capsules penicillin in oil, and (3) Penicillin with aluminum hydroxide gel

Tablets or capsules buffered penicillin contain one or more of such buffer substances as sodium citrate, citric acid, aluminum hydroxide, calcium carbonate, magnesium oxide and aluminum dihydroxy amino acetate The potency of each tablet or capsule is not less than 20 000 units and the number of tablets or capsules in each single package is such that the total number of units therein is not less than 300 000

Capsules penicillin in oil is a suspension of sodium penicillin or calcium penicillin in refined vegetable food oil The potency of each capsule is not less than 20 000 units and the number of capsules in each single package is such that the total number of units therein is not less than 300,000

Penicillin with aluminum hydroxide gel is a combination package of sodium or calcium penicillin and aluminum hydroxide gel The quantity of aluminum hydroxide gel packaged with the penicillin shall be 30 c c for each 100 000 units

Conditions for Which Penicillin Is the Best Therapeutic Agent Available

1 All staphylococcic infections with and without bacteremia
   - Acute and chronic osteomyelitis
   - Carbuncles—soft tissue abscesses
   - Meningitis
   - Cavernous and lateral sinus thrombosis
   - Pneumonia—empyema
   - Carbuncle of kidney
   - Wound infections—burns
   - Endocarditis

2 All cases of clostridia infections
   - Gas gangrene
   - Malignant edema

3 All hemolytic streptococcic infections with bacteremia and all serious local infections
   - Cellulitis
   - Mastoiditis with intracranial complications i e meningitis, sinus thrombosis etc
   - Pneumonia and empyema
   - Puerperal sepsis
   - Peritonitis
   - Endocarditis

4 All anaerobic streptococcic infections
   - Puerperal sepsis
   - Localized infections elsewhere

5 All pneumococcic infections of
   - Meninges
   - Endocardium
   - All cases of sulfonamide resistant pneumococcic pneumonia

6 All gonococcic infections

7 All cases of anthrax

8 All cases of chronic pulmonary suppuration in which surgical treatment is contemplated

9 All meningococcic infections failing to respond to sulfonamides

10 All cases of bacterial endocarditis due to susceptible organisms

11 Erysipeloid (swine erysipelas)

12 Vincent's infection

13 Prophylactic use in prevention of possible secondary infection following tonsillectomy and tooth extraction in cases with a history of rheumatic fever or in rheumatic heart disease in congenital heart disease and in other conditions in which secondary infection may occur (infected teeth tonsils)

Conditions for Which Penicillin Is Effective but Its Position Is Not Clearly Defined Penicillin while effective in the treatment for the following diseases will require additional experimental work before its position is clearly defined

1 Syphilis

2 Actinomycosis

3 Diphtheria in conjunction with antitoxin

Conditions for Which Penicillin Is of Questionable Value Penicillin is of questionable value in mixed infections of the peritoneum

and liver in which the predominating organism is of the gram negative flora, i e

1 Ruptured appendix with peritonitis
2 Liver abscess
3 Urinary tract infections due to Escherichia coli
4 It is also of questionable value in rat bite fever due to Streptobacillus moniliformia

Conditions for Which Penicillin Is Contra indicated Penicillin is ineffective for the following

1 All Gram negative bacillary infections
   Typhoid paratyphoid
   Dysentery
   Escherichia coli
   Hemophilus influenzae
   Bacillus proteus
   Bacillus pyocyaneus
   Brucella melitensis
   Pasteurella tularensis
   Friedlander s bacillus
2 Tuberculosis
3 Toxoplasmosis
4 Histoplasmosis
5 Acute rheumatic fever
6 Lupus erythematosis diffuse
7 Infectious mononucleosis
8 Pemphigus
9 Hodgkin s disease
10 Acute and chronic leucemia
11 Ulcerative colitis
12 Coccidioidomycosis
13 Malaria
14 Poliomyelitis
15 Blastomycosis
16 Non specific iritis and uveitis
17 Moniliasis
18 Virus infections
19 Cancer
20 Yeasts and molds

Specific Treatment and Dosage Schedule The dosage of penicillin will vary from one patient to another depending upon the type and severity of the infection The objective in every case is to bring the infection under control as quickly as possible In most cases a minimum of 100 000 units daily will be required Penicillin is excreted rapidly in the urine following a single injection so that it is frequently impossible to detect it in the blood for a period longer than two to four hours It is advisable therefore to use repeated intramuscular or intravenous injections every three or four hours, or to administer it as a continuous infusion

Considerable stress has been placed on minimal dosage in the literature While the majority of patients respond to minimal doses a continuance of such a philosophy suggests two possible dangers (a) penicillin resistant strains may be developed and disseminated and (b) an infection may be controlled but not eradicated The following recommendations are made (October 1945) with a full realization that as experience accumulates revision may be necessary

A *Serious infections with or without bacteremia*—an initial dose of 15 000 or 20 000 Oxford units with continuing dosage as

1 Constant intravenous injection of isotonic solution of sodium chloride containing penicillin so that 5 000 to 10 000 Oxford units is delivered every hour, making a total of 120 000 to 240 000 units in a twenty four hour period One half of the total daily dose may be dissolved in a liter of isotonic solution of sodium chloride and allowed to drip at the rate of 30 to 40 drops per minute

2 If a continuous intravenous drip is undesirable, 20 000 to 40 000 units may be injected intramuscularly every three or four hours

3 After the temperature has returned to normal the penicillin may be continued as long as there are any signs of active infection In many infections such as meningitis bacterial endocarditis and osteomyelitis it has usually been necesary to continue treatment for one or more weeks after apparent clinical recovery

B In chronically infected compound injuries osteomyelitis and the like the dosage advised is 20 000 units every two hours or 40 000 units every four hours parenterally with local treatment as indicated This dosage schedule may have to be increased depending upon both the seriousness of the infection and the response to treatment The best results are obtained in these cases when penicillin is combined with adequate surgical treatment

C Gonorrhea

1 25 000 units every three hours intramuscularly for five doses The results of

treatment should be controlled by culture of exudate All patients failing to respond to the first course should be retreated

2 *Penicillin in oil and wax* 300 000 units as a single injection or 200,000 units as a initial injection followed by 100 000 units in twelve hours, or three injections at eight hour intervals of 100 000 units each In the presence of complications such as arthritis, endocarditis and epididymitis the dosage should be intensified and prolonged

3 *Oral penicillin* 40 000 to 50 000 units every two to three hours for six doses per day for one or two days

Combined Therapy A single injection of 100,000 units followed not later than two or three hours by oral doses of 40 000 to 50 000 units each every two or three hours for six doses per day for one or two days In complications such as arthritis endocarditis or epididymitis penicillin should be administered parenterally *Always consider concurrent infections of gonorrhea and syphilis* and the possibility of masking the chancre by the foregoing dosage schedule Blood serologic tests should be made once a month for at least three months

D Empyema

1 Penicillin in isotonic solution of sodium chloride should be injected directly into the empyema cavity after aspiration of pus or fluid This should be done once or twice daily using 50 000 or 100 000 units depending upon the size of the cavity the type of infection and the number of organisms Where possible the abscesses should be aspirated rather than incised since it is desirable to maintain the cavity into which the drug has been injected Penicillin solution is not practical for irrigations since it requires at least 6 to 8 hours for the maximum effect of a given dose and contact is necessary When the exudate is thick it is frequently necessary to employ thoracotomy to insure adequate drainage Once the cavity is drained it can be kept sterile by injecting penicillin into it daily

2 Chemotherapeutic measures should not delay surgical drainage of empyemas It is not practical to persist in penicillin therapy for two or three months in an effort to cure an established empyema without drainage, since a thoracotomy will eventually be needed Instead, one should make vigorous attempts to prevent the empyema during the first few weeks following the onset of the infection and then stop the drug In case the empyema has not been completely prevented drainage will be necessary, for as Poppe (47) has shown in some 150 cases, penicillin does not alter the surgical principles of treatment in any way Pus must be drained after it is definitely established

Penicillin should be administered during the incipient stages of pleural infections or better before a pleural effusion has developed Positive cultures and the formation of fluid should decrease within a few days if the treatment is going to be successful The drug is given both by the parenteral and intrapleural route in daily dosage of over 100 000 units parenterally combined with an equal or greater amount given intrapleurally

3 Patients apparently "cured of their empyemas by penicillin should be watched for possible recurrences A small group of patients so treated develop empyema despite large amounts of penicillin administered during the incipient stages of infection They may remain afebrile and asymptomatic with clear sterile pleural fluid until about one week following the termination of penicillin therapy Suddenly they develop all the signs and symptoms of an acute empyema Excellent results follow the usual surgical drainage

E Meningitis

1 Penicillin does not penetrate the subarachnoid space in appreciable amounts so that it is necessary to inject penicillin into the subarachnoid space or intracisternally in order to produce the desired effect Either the sodium or the calcium salt may be used 10 000 units diluted in isotonic solution of sodium chloride in a concentration of 1 000 units per c c should be injected once or twice daily depending upon the clinical course and the presence of organisms

It appears that in the treatment of Group I meningococcus meningitis the sulfonamides are the drugs of choice penicillin may be effective but the response is less favorable than that from sulfonamide therapy Sulfadiazine appears to be the drug of choice in

the treatment of meningococcal meningitis There are reports however of cures by penicillin after the sulfonamides have failed

Penicillin has been effective in decreasing the mortality rate in *pneumococcal meningitis* In 53 reported cases there were 15 deaths a mortality rate of 28 per cent Most workers agree that the sulfonamides should be used in conjunction with penicillin

2 It is difficult to properly evaluate the value of penicillin in the treatment of syphilis of the nervous system from the reports in the literature since but few cases have been treated and none have been followed for a sufficiently long interval to determine the final results To further complicate matters many workers have not felt justified in withholding other forms of therapy while giving penicillin

Nelson and Duncan (48) have shown that in cases of acute syphilitic meningitis the intramuscular injection of penicillin in dosages varying from 600 000 to 4 000 000 units was effective in relieving symptoms and in producing improvements in the abnormalities in the cerebrospinal fluid

F Bacterial Endocarditis

1 Penicillin is the best agent available for the treatment of bacterial endocarditis Penicillin alone is as effective as penicillin combined with heparin The treatment should be continued for three weeks or longer depending upon the individual case Intermittent intramuscular injection at 2 or 3 hour intervals is the most convenient and satisfactory method of administration although in a few cases the continuous intravenous route may be desirable to obtain the maximum effect If best results are to be obtained the daily dosage should be from 200 000 to 300 000 units The infecting organism must be susceptible to penicillin if a favorable response to treatment is to be expected (46)

2 In 50 per cent of cases the infection responds promptly and apparently permanently to one course of treatment In the remainder of cases various complications may be expected These include death from conditions not responsive to chemotherapy failure to respond to the usual doses of penicillin or the reappearance of symptoms and bacteremia either immediately after the completion of treatment, or at a later date If the blood culture remains sterile after the completion of treatment the persistence of fever splenomegaly leucocytosis embolic phenomena and an elevated sedimentation rate does not necessarily mean that therapy has been unsuccessful

3 What is the criteria of cure? Until more experience is available the formulation of precise criteria cannot be made It appears advisable to wait until the patient has had negative blood cultures and has been free of symptoms for at least a year before considering him cured Reinfection may occur at any time after the original infection has been eradicated and it is not unlikely that multiple attacks of subacute bacterial endocarditis may be observed in the future

Precautions Administer penicillin *only parenterally* in meningitis endocarditis and peritonitis In acute infection with bacteremia or septicemia parenteral administration of penicillin should be continued until the blood cultures become negative and the acute condition is controlled (32) (46)

Other Uses for Penicillin in Oil and Wax

Pneumonia and Acute Staphylococcic and Streptococcic Infections — A minimum of 300 000 units daily preferably in divided doses and continued until the temperature returns to normal and other evidence of infection disappears Preparations containing 200 000 units per c c may be given at twelve hour intervals If the quantity is 100 000 units per c c administration at eight hour intervals is necessary Rotation of the sites of injection is desirable

Other Uses for Oral Penicillin

Pneumococcic Streptococcic and Staphylococcic Infections —In these infections a minimum of 20 000 to 40 000 units parenterally is advised every three hours After the acute phase and when the temperature has receded the treatment may be continued using oral penicillin The dosage advised is 40 000 to 50 000 units each two or three hours (day and night) for at least forty-eight hours after the

temperature has returned to normal If the condition is not controlled by oral penicillin, return to parenteral administration (32) (34) (35)

McDermott and his group treated forty five patients with pneumococcic pneumonia using orally administered penicillin They report only one death and one serious complication, an empyema The results therapeutically were comparable to those observed in the treatment of pneumococcus pneumonia using the intramuscular route for penicillin They used 750,000 units on the first day and from 400,000 to 600 000 units on subsequent days of therapy To diminish the possibility of relapse they advise prolonging therapy for 7 or more days depending upon the severity and the duration of the infection

Uses for Topical Penicillin Products

Penicillin Ophthalmic Ointment This ointment is of value in superficial infections of the eye involving the cornea conjunctiva meibomian glands and lacrimal sac caused by organisms susceptible to penicillin The ointment should be applied locally once or twice daily as the condition indicates Local treatment of gonorrheal conjunctivitis should be supplemented in all cases with parenterally administered penicillin If sensitization occurs discontinue use immediately

Penicillin Ointment This ointment may be used for superficial infections of the skin caused by organisms susceptible to penicillin It is applied locally, with or without a bandage one or more times daily as the condition indicates If the condition warrants supplement the local treatment with parenteral administration of penicillin If sensitization occurs discontinue use of the drug immediately

Penicillin Troches In Vincent s infection allow one troche to dissolve in the mouth Repeat two or three times a day between meals Smears should be taken before and after therapy If indicated supplement the local treatment with oral treatment If *masticatory* troches are used chew two or three daily and if high continuous concentrations are desired chew one troche each hour or two Discontinue immediately if sensitization occurs

Aerosol Penicillin The administration of drugs by inhalation has been employed for many years in patients with asthma and pulmonary emphysema Penicillin aerosol was suggested by Bryson, Sansome and Laskin in 1944 (50) Since the drug was known to be bacteriostatic in extremely high dilutions inhibiting the growth of hemolytic streptococci in quantities as low as 0 01 microgram per c c the potential value of penicillin aerosols was considered likely The average physician in general practice is not utilizing the full potentialities of penicillin probably because of the present need of frequent and regular administration and its concomitant difficulties

Aerosol penicillin has been shown to be a valuable substitute and adjunct for the usual techniques of administration It is especially efficacious in both acute and chronic upper respiratory infections being more effective than parenterally administered penicillin It can be used at home as well as in the office for continuous or intermittent administration Studies have shown that penicillin is readily absorbed from the lungs, high blood levels being attained when long slow breathing with a pause before exhaling is practiced The aim of treatment however is not a high blood level but a local application of penicillin on the bronchial wall

Using the technique described by Barach (38) Bryson (50) Knott and Clark (42) and Vermilye (39) the highly antibiotic penicillin is brought into close contact with the actual infecting organism, analagous to the injection of penicillin solution into empyema cavities or into the spinal fluid in meningitis The drug, preferably the calcium salt is dissolved in sterile isotonic solution of sodium chloride in such amounts that 1 c c contains from 25 000 to 50 000 units Utilizing a special nebulizer (Vaponefrin Co Upper Darby Pa) which is connected to an oxygen tank arranged to pass 5 to 8 liters per minute the penicillin is inhaled as a fine mist three to five times daily at three to four hour intervals Automatic production of penicillin aerosol only during the inspiratory cycle is possible by utilizing a specially constructed valve Small ordinary nebulizers may also be employed providing the particles produced are under 1 micron in diameter such as the Vaponefrin or the De

Vilbiss No 40 neubilizer The mouth of the nebulizer can be placed either in the mouth or the nose A positive pressure oxygen mask may be attached to the nebulizer containing the penicillin solution and utilized for babies or adults for whom the continuous inhalation of oxygen is also desired to prevent pulmonary edema It is also possible to administer nebulized penicillin through a catheter directly into infected antrums or sphenoid sinuses after a preliminary evacuation and irrigation

In *sinusitis* preliminary administration of neosynephrine or privine nose drops is advised to open the sinuses In *asthma* or other conditions causing bronchospasm 0 5 c c of 0 25 per cent neosynephrine should first be inhaled from the nebulizer so that subsequent inhalation will be more effectively brought into contact with the desired area The use of penicillin as an inhalant must not be confused with vaporization methods in which case the heat employed would inactivate the penicillin

Cases Suitable for Aerosol Penicillin Therapy

1 Acute primary invasions of respiratory tissues with and without pneumonitis
   a Pneumococcus types
   b H Streptococcus and staphylococcus types
   c Virus types with secondary invasions of H streptococci staphylococci and nonhemolytic streptococcus MG group
2 Persistent bacterial infections of the upper respiratory tract due to pneumococci *H streptococci and staphylococci with acute pneumonic episodes without allergic* manifestations
3 Similar bacterial infections which develop into bacterial allergies in the constitutionally nonallergic patient
4 Similar bacterial infections which develop into bacterial allergies in those with an allergic type constitution in combination with other extrinsic allergies
   a Sinobronchitis
   b Eczema
   c Migraine
   d Asthma
5 Chronic upper respiratory bacterial infections in allergic and nonallergic subjects
6 Upper respiratory infections leading to glomerulonephritis and hypertension sinusitis with nephrosis and myocarditis with and without hypertension

Rapid clinical improvement has been noted in intrinsic bacterial asthma In some cases recurrences of attacks were treated by a second course which resulted in complete relief It may be that a combination of penicillin injected intramuscularly to provide a high blood level combined with the inhalation of penicillin aerosol will be the procedure of choice in patients with bronchial asthma as well as those with lung abscess chronic bronchitis and bronchiectasis The amelioration and often the elimination of such manifestations as migraine hypertension chronic fatigue gastrointestinal disturbances and fibromyositis with the removal of chronic bacterial infections of the upper respiratory tract by the use of aerosol penicillin are so startling that they must be observed to be believed (39) This is not so unreasonable if we remember that migraine eczema rosacea duodenal duodenal pain allergic colitis extreme fatigue and psychoneurotic symptoms may be due to or aggravated by allergy to the presence of an acute or chronic upper respiratory infection

In the nonsurgical treatment of *bronchiectasis* Strieder (40) reports that such inhalations have caused the foul sputum to clear up within a few days to a week following institution of therapy While as yet there are not enough cases reported to be of clinical or statistical significance this method deserves wide trial

Side Effects of Aerosol Penicillin Barach and his group administered aerosol penicillin to 20 patients for periods of from 7 days to one month and report no convincing evidence of an irritant effect on the lungs A few patients reported substernal soreness for a few days Other workers have found that if an aerosol penicillin treatment is given simultaneously or within a few hours of a pollen immunization or vaccine a severe allergic reaction may develop (39) It is characterized by acute abdominal pain urticaria nervousness and angioneurotic edema It can be readily controlled by *isonipecaine* 50 mg given either orally or parenterally

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CHAPTER XIX

GERIATRICS THE CARE OF THE AGED

General Considerations

Geriatric medicine has been defined (1) as that branch of medical science which treats of the elderly in all their physiologic and pathologic relations Its problems are not confined to those patients actually senile for the infirmities and disorders of later years arise insidiously far earlier than their clinical manifestations The aged are different persons both physically and mentally from what they were in their youth and maturity and it should be recognized that the symptoms signs pathogenesis course therapy and prognosis of their diseases are all altered by the biological changes of aging

The increase in life expectancy since 1909 is little short of dramatic There are more people today between 20 and 65 and fewer under 16 than ever before There is no doubt that the casualties of the present conflict will still further accentuate the trend toward an aging population The increase in the number of the aged can be attributed to a decrease in the infant mortality rate control of infectious diseases better living conditions the high standards of sanitation and a decline in the birth rate

Physiologic Changes of Senescence

According to Piersol (2) there are certain changes occurring in the aged which can be considered as physiological Among them are (1) graying of hair (2) atrophy of the lymphoid tissues (3) decrease in vital capacity from the senile type of emphysema (4) osteoporosis of the long bones and an increase in the size of the flat bones (5) arcus senilis (6) atrophy of the intervertebral discs with a resultant decrease in height (7) decrease in the papillary beds of the skin which causes a pallor often mistaken for anemia (8) decrease or absence of the deep tendon reflexes and (9) atrophy of the visceral organs excepting the heart

Pathologic Changes in the Aged

The degenerative disorders which take greatest toll in the aged have scarcely been affected by the advances of preventive medicine In fact, their mortality rate has risen The degenerative diseases with the highest incidence are cardiovascular disease, arteriosclerosis nephritis cerebral hemorrhage diabetes and cancer The commonest cause of death in patients past fifty years of age are heart disease cancer, nephritis pneumonia influenza and tuberculosis

The average adult patient cares little about seeking any form of preventive medicine or treatment especially if it requires any time effort or expense on his part He is usually content to carry on without medical advice then when he becomes ill he is likely to demand miracles which a little foresight and thought would have prevented

Thewlis (3) lists measures which may be undertaken to prevent specific diseases Among them are

1 Early treatment of precancerous dermatoses (See page 1011)
2 Education of the diabetic to avoid complications (See page 1090)
3 Warning against common hazards
4 Liver therapy for pernicious anemia to prevent degenerative changes in the cord
5 Avoidance of sudden strain to prevent attacks of coronary thrombosis
6 The earlier diagnosis of gastric lesions by gastroscopy and gastro photography
7 Removal of foci of infections
8 General and mental hygiene
9 Proper nutrition
10 Postponing operations until senescence when the risk is greater than at earlier ages

The aged patient is frequently difficult to treat and it requires much patience from one who is genuinely interested in him Such patients are often unwilling to be hospitalized, and as Thewlis has pointed out it is frequently necessary to perform operations in their homes In many with irreparable organic changes relief should be the keynote of treatment and

since the elderly tolerate pain better than their younger brethren, smaller quantities of sedative can be used One of the commonest causes of psychotic behavior in the aged is the indiscriminate use of the barbiturates since there is an increased capillary permeability in cerebral arteriosclerosis The barbiturates are metabolized slowly and therefore have a prolonged effect Codeine and whisky are good sedatives for the aged Other causes of psychotic behavior often overlooked are urinary retention in one with prostatic hypertrophy, then the blood urea nitrogen becomes elevated from the retention of the nitrogenous products More rarely, mental symptoms result from over dosage of digitalis Hospitalization may also have unfortunate psychic effects on elderly patients and the strange environment may cause undesirable reactions Prolonged rest in bed is detrimental especially if there is myocardial degeneration and the inactivity and *prolonged recumbency may cause a hypostatic* pneumonia It is therefore well to keep these patients in a chair when possible in order to prevent both the pneumonia and profound mental depression Rest in bed however should be obligatory for those with transient hypertensive crises and fevers of unexplained origin

Drugs are absorbed more slowly in the aged and frequently have a cumulative effect It must always be kept *in mind that they should* function at their own level as much harm can result from attempting to bring them to the functional level of a younger person through *various medications which are tolerated poorly* Attempts to bring a pronounced hypertension down to normal levels often ends disastrously The same can be said for the diabetic who has adapted himself to a blood sugar level above normal and is suddenly subjected to measures aimed at bringing the level down to normal in a short time

Anti-Syphilitic Treatment in the Aged

If a positive serologic reaction for syphilis is found in a routine blood examination on an aged person, there is no point in treating him A patient who has been able to survive to 70 years with a positive serologic reaction should not be treated at all and all patients over *fifty years* of age should be treated cautiously if at all

Cardiovascular Disease in the Aged

Heart disease is discussed in detail in Chapter 5, therefore only those points pertinent to the management of cardiac disease in the aged will be touched on here There is no way to determine abnormal cardiovascular ageing except by finding definite cardiac enlargement, calcific aortic stenosis, persistent hypertension, signs of congestive failure, a loud persistent apical systolic murmur, abnormal cardiac rhythms EKG signs of conduction defects or angina pectoris in the absence of anemia thyrotoxicosis or syphilis

DIMINISHED CARDIAC RESERVE

The symptoms of a diminished cardiac reserve are a tightness under the sternum and shortness of breath, there may be a slight hypertension, or it may even be normal or low The physical examination and roentgen study may be within normal limits Exertion may bring on this distress, and it is frequently of value to advise the patient to avoid exertion and to seek a short rest period after meals as well as to live a less strenuous emotional life The purine bases are of value since the underlying difficulty is based upon an insufficient coronary flow Digitalis should be avoided unless circulatory failure is present

ANGINAL PAIN UPON EXERTION

Pain following exertion may frequently be disabling Electrocardiographic studies may confirm the presence of coronary heart disease There frequently is extensive damage as well as hypertension One type of exertion may provoke severe discomfort while another one almost as strenuous may cause no symptoms Each patient is an individual problem

Treatment

It may be well to allow the patient to continue at his occupation but one should have a frank discussion with him in which certain rules of a way of life should be set forth He should rest after meals as a greater coronary flow is required after eating and to put additional demands upon it creates a situation which cannot always be met Excitement arguments straining at stool and sexual intercourse are fraught with danger For the immediate pain *nitroglycerin* is advised As

the vasodilator action of the nitrites is evanescent enteric coated *aminophyllin* may be tried as it gives satisfactory results in some cases *Phenobarbital* is a good drug to relieve emotional tension but the cumulative action of the barbiturates should be remembered

Those cases with hypertension should be treated with moderation One should not try to lower the blood pressure for the increased blood pressure makes for an increased coronary flow which the enlarged muscle mass calls for Here the increased blood pressure is not an unmixed evil The use of potassium thiocyanate is not without danger in aged patients

ABNORMAL CARDIAC RHYTHM

Extrasystoles These demand no special treatment By careful attention to the bowel habits diet and tobacco ectopic beats may be abolished If these beats increase and become a mental hazard the coronary flow should be increased by aminophylline It is unwise to pay too much attention to them

Sinus Tachycardia The treatment of sinus tachycardia is that of the underlying cause which is commonly extracardiac such as febrile diseases or toxic states Digitalis should not be used unless congestive heart failure is present

Sinus Bradycardia This is common in aged people who are in good health It is possibly due to a decreased sensitivity of the sinus node and to a decreased body metabolism It can be caused by toxic states and gastrointestinal reflexes It is differentiated from heart block by the fact that the heart rate can be accelerated by a change in posture or by exercise As a rule no treatment is necessary but if it is desired to increase the heart rate atropine may be tried Bradycardia is no contra indication to the use of digitalis where it is indicated

Auriculoventricular Block Diagnosis is seldom difficult for the pause which occurs when a beat is missed has a time value of approximately two cycles of the basic rhythm The P wave of the dropped beat occurs in its normal relationship but it is not followed by a QRST complex

Treatment is not required although the underlying myocardial disease should receive appropriate attention Digitalis is contra indicated and should be stopped if it is the cause

Complete Heart Block Complete heart block is diagnosed by a slow cardiac rate not appreciably altered by exercise In the EKG the P waves and the QRST complexes occur at regular intervals but without any semblance of time relationship to each other The xanthine and ephedrine group of drugs should be given as for a Stokes Adams attack Digitalis is not contraindicated as it has no effect on the pacemaker of the ventricles

Auricular Fibrillation This is very common in the aged being present in about 4 per cent of persons over seventy years The diagnosis is made on the finding of complete irregularity of the ventricular rhythm The P waves of the EKG are replaced by small irregular waves Once the rhythm has become established little good will be accomplished by trying to abolish it A normal rhythm is best but it is unwise and not good judgement to attempt to obtain such a rhythm and run the risk of inducing heart failure The usual treatment is *digitalis* in sufficient dosage to keep the ventricular rate within normal limits If the rate is 85 or less, treatment may not be necessary *Quinidine* is used in the course of auricular fibrillation associated with myocardial infarction

ACUTE CORONARY OCCLUSION

This is a major emergency in the aged Pain over the precordium falling blood pressure leucocytosis fever friction rub and an increased sedimentation rate are present in typical cases Rest in bed and the administration of oxygen at once are indicated if the diagnosis is certain Do not wait for cyanosis and dyspnea to make their appearance *Papaverine* increases the coronary flow and does not augment vagus activity When it does not control coronary pain its use will permit a reduction in the amount of morphine used *Morphine* augments vagus activity and it may accelerate reflex coronary constriction It has no effect on the coronary volume *Atropine* blocks the vagus nerve and when reflex coronary constriction is a dominant factor it may be used to good advantage *Aminophylline* given intravenously is preferred by some to atropine for pulmonary edema or dyspnea The general nursing care and supportive treatment is the same as that mentioned in the discussion of coronary heart disease on page 263 with the exception that in

the aged it is sometimes better to shorten the period of rest in bed

Pulmonary Complications in the Aged

CHRONIC BRONCHITIS

Chronic bronchitis is a frequent complication of pulmonary emphysema which is seen in practically all aging people It frequently progresses to bronchiectasis There is no specific treatment and the therapy is purely palliative Bronchial secretions may be liquified and induced to flow more freely by steam inhalations and hot drinks Inhalants and expectorants are of doubtful value The direct inhalation of nebulized *neosynephrin* 1 100, may relieve bronchospasm For dyspnea and anoxemia, a special nebulizer can be had which is attached to the oxygen tank, oxygen carrying nebulized neosynephrine can thus be carried into the oroopharynx *Codeine* may be used for the cough Other drugs which may be used are dilute hydrocyanic acid, Dover s powders ammonium chloride menthol vapors and potassium iodide Rest in bed with protection from cold dust and changes of temperature are beneficial The prognosis is not favorable for those having to remain in the temperate zone

PULMONARY FIBROSIS

Pulmonary fibrosis is very common in the aged and represents a long succession of common respiratory inflammations rather than any single previous severe infection Bronchopneumonia may leave a fibrosis, and the tubercle bacillus may be responsible for both localized and diffuse fibrosis of the lungs Other causes are pneumoconiosis and the inhalation of irritating gases and fumes Fibrosis definitely predisposes the patient to bronchitis and bronchopneumonia Treatment is unsatisfactory Some advise breathing exercises, the wearing of a belt if the abdominal wall is pendulous and atonic and climatotherapy The last mentioned is seldom feasible as these folks can as a rule ill afford to winter at spas and watering places

CHRONIC PULMONARY EMPHYSEMA

This condition is seen in practically all aged people and is usually associated with fibrosis chronic bronchitis and adhesive pleurisy There is an increased air content in the lungs, but the air is static and the gaseous exchange permanently and later fatally impaired The elastic elements weaken, and as a result of inflammatory processes, later break down, the alveolar septa eventually disappear Inspiration is carried on with great effort and expiration is not adequate, which results in permanent overdistension of the alveoli and decreased elasticity of the pulmonary tissues As this progresses, the lungs can no longer resist the traction of the chest wall, and distend until a position approaching full inspiration is reached Deflation is not possible during the expiratory phase by the normal passive recoil of the lung tissues it has to be actively compressed by the extrinsic muscles of expiration The diminution of the capillary bed in the pulmonary circuit imposes increa ed burden on the right heart Right ventricular hypertrophy, dilatation and heart failure follow The heart is small and mid thoracic in type Cyanosis deepens dyspnea and chronic passive congestion ensue The onset of congestive failure is ominous, the course then resolving into a series of alternate episodes of improvement and congestive failure The failure does not always respond to digitalis since the emphysema remains

Treatment

No treatment will restore normal function The patient should be removed from dust and temperature changes An abdominal binder may be beneficial if the abdomen is pendulous and atonic Oxygen is of value and can be given one hour before bedtime

PNEUMONIA

The pneumonias are discussed more completely in Chapter IX therefore only those points pertinent to the management of the pneumonias in the aged will be mentioned here

Bronchopneumonia Senile Atypical Hypostatic Terminal Pneumonia

While modern methods of therapy such as the sulfonamides and penicillin have achieved a great decrease in the mortality of pneumonia, the deaths from pneumonia in the aged population is far out of proportion to the reduction in mortality in the whole group of pneumonias

The diagnosis is frequently difficult in the early stages due to the insidious onset, uncertain physical signs, irregular course and the variability of causes Even a minor cold may be followed by periods of prostration, there may be an unexplained illness without rusty sputum or chills or findings in the lungs the patient may be near death before the diagnosis is made As a rule when dyspnea cyanosis and rales are present and when fever lasts longer than four days associated with marked constitutional symptoms pneumonia should be suspected Roentgen study of the chest is of inestimable value Such clinical entities as infarction atelectasis bronchiectasis, pulmonary congestion plugging of the bronchi pleural exudate and peripneumonitis may simulate atypical pneumonia This type of pneumonia is differentiated from pneumococcal lobar pneumonia by its insidious onset irregular course and fever curve the location of the rales, absence of signs of consolidation and infrequency of rusty or bloody sputum pleurisy and herpes

Treatment Frequently in this group of pneumonias typical pneumococci are not found where they can be typed early penicillin or sulfonamide treatment should be instituted without delay Recent studies indicate that penicillin will entirely supplant anti pneumococcic serum in cases where the serum was formerly employed Nursing care is essential and when possible the patient should be taken to a hospital This should be done preferably early in the condition As a rule these older patients do better when propped up in a semi sitting position Absolute rest with a minimal number of examinations after the diagnosis has once been established should be the rule Oral hygiene is frequently neglected by the aged patients They should have their teeth attended and they should brush their teeth daily using alkaline mouth washes liberally Tepid sponge baths may be given several times daily for fever or restlessness The bowels are kept open with mineral oil or enemas every other day Many of these patients for years have been accustomed to take a daily cathartic and complain of auto intoxication if they do not have their daily bowel movement

Oxygen therapy is of great benefit in the early stages before the inflammatory exudate has had a chance to collect In cases of pulmonary edema it is frequently given under positive pressure with good results The oxygen flow should be regulated at from 4 to 6 liters per minute if a catheter is used and from 6 to 8 liters per minute if the patient is in a tent

The *diet* should consist of small frequent meals of hot and nutritious simple foods starting with soups broths milk toast and fruit juices Later chicken eggs ground meat, chops custards, junkets and mashed potatoes can be added There is no contra indication to coffee or tea and the patient should be urged to drink plenty of water Carbonated drinks such as coca cola or ginger ale are beneficial when there is nausea Whisky is of definite value and is used in chronic alcoholics to stave off delirium tremens It is best given in the manner preferred by the patient In the dehydrated patient intravenous fluids may be necessary though they may be given as a hypodermoclysis which route is preferred by some physicians because of the slower absorption Judicious use of the hot water bottle the ice bag or the electric pad can do much to bring comfort to the patient Steam tents are useful only when the secretions are not profuse and watery Coughing can usually be controlled by codeine which is superior to cough syrups since these frequently cause nausea

For severe chest pain diathermy a chest binder (not adhesive plaster) or the heating pad should be tried Only as a last resort should morphine be given as tympanites and constipation may follow its use Digitalis is used only for decompensation or auricular fibrillation The rectal tube may be of benefit in abdominal distension prostigmine demerol or posterior pituitary solution (pitressin) are also worthy of trial or a hot water bottle or electric pad over the abdomen There is some debate over the use of warm blankets and heating pads for circulatory collapse It is believed by many clinicians today that such measures including the use of adrenalin increases rather than relieves the condition Coramine is also of dubious value Circulatory collapse is best treated by *oxygen* and *adrenal cortical extract*

Delirium is not infrequent in older patients and calls for constant nursing care lest the patient injure himself A sheet restraint may

be tried Ankle or wrist restraints usually agitate the patient and are of little use Paraldehyde or chloral hydrate should be considered, but the administration of paraldehyde intravenously is not without danger and should not be given to these patients

Pneumonococcal Pneumonia

See page 490

CARCINOMA OF THE LUNG

See page 503

TUBERCULOSIS (PULMONARY)

See page 462

PNEUMOCONIOSIS

See page 520

MYCOTIC INFECTIONS OF THE LUNG

See page 508

Gastrointestinal Diseases in the Aged

In the aged patient we see physiological changes incident to the involution associated with senile atrophy Achlorhydria increases with advancing age and there is a decrease in the amounts of saliva and ptyalin formed In spite of this, however the aged have no difficulty in the digestion of carbohydrates There is no basis for restricting the protein intake of older people *As a general rule they should be* left to their own selection of foods Due to *the ageing process of the taste buds a loss of* appetite is not unusual To this can be added the possible factor of a diminution in sight and smell, and changes in hunger contractions Vitamin B is reported to be effective in stimulating the appetite as are bitters and alcoholic drinks

Many of the aged are much concerned over the appearance of their tongue believing it to be a general index or mirror of the state of their bowels and general health It might be mentioned in passing that glossitis is associated with (1) nutritional or vitamin deficiency (2) the Plummer Vinson syndrome (3) pernicious anemia (4) achlorhydria and (5) psychogenic sore tongue

CARCINOMA OF THE STOMACH

This disease must always be considered when there is any digestive discomfort related to the ingestion of food Unfortunately the symptoms are rarely present until the tumor has grown large enough to impair normal gastric function or produce pain from ulceration Males between forty and sixty years of age are most frequently affected The reader is referred to page 83 for a more complete discussion

PEPTIC ULCER

This may be acute or chronic, and may persist for years The death rate becomes progressively higher with age up to 75 years Symptoms have begun in patients past 60 years There is a group of ulcers which is secondary to disease of the liver, or gallbladder or accompanies cardiac renal or prostatic disease *Gastric ulcer is serious in the aged,* for arteriosclerosis of the gastric vessels is conducive to serious, protracted bleeding It should be remembered that while 50 to 60 per cent of all gastric carcinomas are associated with achlorhydria, *free acid may be present* Free hydrochloric acid may be diminished in gastric ulcer but its absence in duodenal ulcer is unknown Gastroscopy in the hands of the experienced may be of assistance in the diagnosis Roentgen study is invaluable, but it should be supported by clinical and laboratory evidence as an ulcer defect without spasm or signs of irritability may be an old healed lesion

Beware of indigestion masking heart disease Old people with arteriosclerosis of the coronary arteries may have the clinical symptoms of peptic ulcer particularly the postprandial distress and constriction in the chest In these cases the administration of nitroglycerin, grains $\frac{1}{100}$ often brings immediate relief As a rule no benefit is derived from alkalies

For further discussion on the diagnosis and treatment see page 73

APPENDICITIS

Appendicitis is mentioned only here to point out that it may occur in the aged although it is seldom considered as a possibility mesenteric occlusion or intestinal obstruction being thought of first Statistics show that the mortality in appendicitis in those above fifty five years has increased As a rule the symptomatology is bizarre and suggests almost any disease except appendicitis To rely on the classical symptoms is to court disaster

Nausea, vague digestive disturbances diarrhea or constipation may be the first symptom The nausea is likely to persist Localization of pain is notoriously slow as compared with that in younger patients It may be in the left side as a result of back pressure and distension of the terminal ileum Pain on pressure over the appendix is usually present A rectal examination should be made The pain of fissures or hemorrhoids should not mislead one A twenty four hour motor meal or barium localization enema may be of diagnostic aid when there is doubt The normal appendix is less likely to fill after a barium enema than following a motor meal As a result of the advances in pre and postoperative care during the last decade the hazards of operation for the aged are less formidable than formerly

GALL BLADDER DISEASE

Cholelithiasis and cholecystitis represent the commonest gall bladder disturbances found in the aged Gall stones have been discovered in about 25 per cent of autopsies in which the stones were unsuspected throughout life Etiological factors in the formation of stones are believed to be stasis infection and hypercholesterolemia Such factors may be present singly or in combination and their influence becomes more effective with advancing age particularly in the female sex It must be remembered that gall bladder disease may mask a cardiac lesion be associated with it or aggravate it In some instances severe disease of the biliary tract occurs with vague and indistinct clinical manifestations until a severe abdominal catastrophe results It is not unusual to see severe inflammatory disease of the abdomen in the aged with little or no pain or constitutional reactions and scarcity of physical signs When there is any question or gall bladder disease a thorough gastrointestinal examination including roentgen studies of the biliary tract and transduodenal biliary drainage should be made An electrocardiographic study should also be included It is better to observe caution in regard to operation in the aged It is unwise to insist on routine surgical procedures for though an aged person may survive the operation he may not be able to withstand some of the postoperative complications which are not uncommon in older patients

The medical management of gall bladder disease is discussed in more detail in Chapter III

CONSTIPATION IN THE AGED

Constipation is common in the aged due to sedentary habits and loss of muscle tone Dietary changes in the edentulous are considered a contributory factor An occasional saline cathartic is of benefit Rectal constipation is the most common form and fecal impaction is not uncommon A bland diet and bulk from vegetable mucilage are more effective than cathartics When false teeth are worn pureed vegetables and vegetable mucilage should be given Metamucil (G D Searle Co) is an excellent product and if taken immediately after dissolving in cold water is free from any offensive taste For fecal impaction an enema of peroxide *well diluted* may be of value

DIVERTICULOSIS AND DIVERTICULITIS

See page 121

Diseases of the Nervous System in the Aged

NEUROLOGICAL FINDINGS OF NO SIGNIFICANCE IN THE AGED

The following neurological findings are commonly present in the aged and no special importance should be attached to them

1 Vibratory sensibility is impaired in the distal portion of the extremities
2 Loss of hearing for high tones as shown by audiometric tests
3 Diminished taste and smell perception
4 Sluggish pupillary reflexes and accommodation
5 Paretic action in oculomotor muscles
6 Ankle jerks are sluggish to absent
7 Flexion of head and trunk
8 Difficulty in relaxing and poverty of movement

MENTAL CHANGES COMMONLY FOUND IN THE AGED

1 A loss of memory in the field of spontaneous recall and for recent events
2 Over loquaciousness with tales of childhood and of olden times'

3 A disturbance of sleep rhythm with nocturnal restlessness Night prowling may result and the patient may go out of doors and suffer accidents
4 Hoarding tendencies with conspicuous detail as to order, or the opposite with marked untidiness
5 Transient periods of confusion
6 Persecutory ideas If the aged person is living with children or in laws these ideas may be basically true
7 Sexual fantasies may take the form of fondling small children
8 Rarely there may be homicidal or suicidal threats if the person is denied his own way

PATHOLOGICAL SYNDROMES COMMONLY SEEN IN THE AGED

Cerebral Arteriosclerosis

See page 946

Senile Dementia

See page 948

Pseudobulbar Palsy

Possibly a better term than pseudobulbar palsy is *supranuclear paralysis* it is an interruption of the cortico bulbar tracts and is a sequel of cerebrovascular accident in the aged particularly if it is bilateral It is characterized by difficulty in swallowing pathological laughing or crying and speech disturbances from paresis of the palate

Senile Paraplegia

There is very little known about this condition

Senile Cerebellar Syndrome

This is also called primary cortical or delayed cortical cerebellar atrophy with a loss of Purkinje cells in the superior and anterior portion of the vermis The patient has difficulty in walking or standing and a staggering gait The lower extremities are chiefly affected There is little or no nystagmus

Parkinson Syndrome

The arteriosclerotic Parkinsonism is somewhat different than the true paralysis agitans It occurs between forty and sixty years and is usually a combination of rigidity and paralysis The onset is sudden and it may follow softening in the region of the basal ganglia Tremor is not as common as in the true paralysis agitans or in epidemic encephalitis The association of pseudo bulbar palsy with the arteriosclerotic type is not uncommon There is a masklike facies with a slow breaking smile When the patient walks, the arms do not swing at the sides in normal fashion but are held flexed or semi flexed at the sides Festination, retropulsion and lateropulsion are common There is a rhythmic tremor which stops on voluntary movement or during sleep The reflexes may be normal There is diminished vibratory sense For the table of differential diagnosis of the Parkinson syndrome, see page 939

Pick s Disease

See page 281

Alzheimer's Disease

See page 948

Diseases of the Skin in the Aged

See Precancerous Dermatoses page 1011

Disorders of the Genitourinary Tract in the Aged

Common pathological conditions encountered in the aged by the gynecologist are *pyuria prolapse senile vaginitis tumors* and *leukoplakic vulvitis*

Pyuria is usually associated with eversion of the urethra caruncles cystoceles or prolapse It is the opinion of many gynecologists that any woman capable of being up and about can withstand such a simple procedure a colpocleisis An associated cystitis should be treated before making the repair In spite of surgical techniques some will have recurrences of their cystoceles rectoceles and prolapse Senile vaginitis is very common in old women it may be associated with caruncle eversion of the urethra or cervical polyps

The commonest genitourinary symptom complex of women consists of urgency frequency bladder irritation dribbling nocturia and pain which is referred over the bladder These symptoms are usually caused by (1)

urethritis (2) cysts or villous formations at the bladder neck, (3) irregularity of the bladder neck, (4) stricture of the urethra (5) urethral caruncle (6) cystocele (7) urethral diverticulum and (8) benign tumors

NON SPECIFIC URETHRITIS

An acute urethritis may be caused by any one of the following (1) too frequent or vigorous instrumentation, (2) difficult labor which causes trauma (3) catheterization using an improperly sterilized catheter (4) presence of foreign bodies and (5) extension of a vaginitis or cystitis

Chronic urethritis in the female is more common than is generally appreciated being more common than in the male The fact that the female urethra is an important portal of entry for infection must not be overlooked Chronic urethritis is usually the aftermath of an acute infection or it may be brought about by (1) a narrowing of the meatus thus interfering with free drainage (2) urethral prolapse and (3) trauma of coitus, masturbation or abnormal practices

Symptoms The symptoms mentioned as a part of the symptom complex may be pronounced There may or may not be a history of gonorrheal vaginitis and it has been found that urethritis may be the result of an infection of the suburethral glands which closely resemble the glands of the prostate

Findings Smears and cultures of the discharge may reveal colon bacilli staphylococci non virulent streptococci trichomonas and diphtheroids Repeated cultures of urine may be negative

Diagnosis A definite diagnosis canusually be made by cystourethroscopy The lumen of the urethra may be narrowed so that the cystoscope is inserted only with difficulty The average caliber of the normal adult female urethra is No 26 French The bougie a boule is used for urethral calibration One per cent *diothane* can be used as a local anesthetic and cystoscopy follow without any discomfort to the patient

Treatment The treatment consists of a bland diet dilatation of the urethra fulguration and the administration of the sulfonamide drugs *sulfathia ole* or *sulfadia ine* Polyps and granulomas are treated by fulguration Other measures commonly employed are the alkalinization of the urine and urinary sedatives Extra urethral foci of infection, especially in the cervix should be eradicated Dilatation is accomplished with straight sounds at weekly intervals increasing the size by one number each week The urethra of women under fifty years of age can be safely dilated up to 32 French Endoscopic applications of silver nitrate while once popular have largely been applanted by sulfonamide therapy

CYSTIC FORMATIONS AT THE NECK OF THE BLADDER

Not infrequently cystic or villous formations are observed upon cystoscopic study of the superior or lateral walls of the neck of the bladder **Treatment** The treatment of choice for cystic or polypoid formations is dilatation followed by an instillation of *mild silver protenate* solution Villous projections are removed by fulguration or by the McCarthy resectoscope *This is not an office procedure* The urine should be kept alkaline *Potassium citrate* will usually relieve the burning upon urination

IRREGULARITY OF THE NECK OF THE BLADDER

In this condition the usual symptoms are difficulty in starting the stream, pain over the bladder area dribbling and the loss of a few drops of urine upon sneezing or coughing It is believed that trauma incident to child birth may play a role in the cause of this condition These patients usually have complete relief of their symptoms following cystoscopy The *treatment* is therefore dilatation of the urethra As these patients are in the older age group it is unwise to carry the dilatation beyond No 28 French

STRICTURE OF THE URETHRA

Contrary to common belief stricture of the female urethra is not uncommon It is found in about 35 per cent of female patients with urinary symptoms Strictures may be *acquired traumatic spasmodic* or *senile* The acquired type are often post gonorrheal they are not uncommon and the majority are located anteriorly The history of the patient usually reveals a progressive urinary difficulty with need for straining to start the stream and diffi

3 A disturbance of sleep rhythm with nocturnal restlessness Night prowling may result and the patient may go out of doors and suffer accidents
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See page 281

Alzheimer s Disease

See page 948

Diseases of the Skin in the Aged

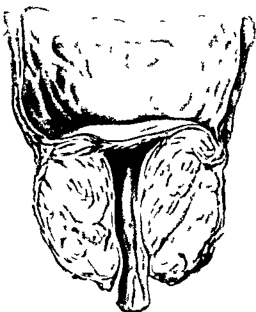
See Precancerous Dermatoses, page 1011

Disorders of the Genitourinary Tract in the Aged

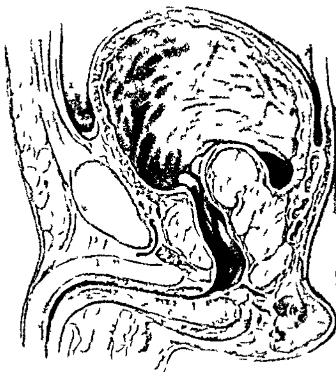
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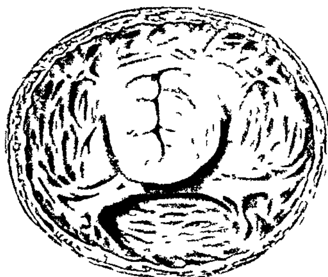
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LATERAL LOBES
WITH MEDIAN
COMMISSURE



MEDIAN LOBE



LATERAL LOBES
WITH MEDIAN
COMMISSURE
(Intra es cal V'ew)

PLATE X
Benign Prostatic Hypertrophy

culty in stopping it. Dribbling may occur after the patient has assumed the erect position.

Diagnosis. Urethroscopy and urethrography are valuable diagnostic aids and will make the diagnosis in every case. Using a bougie a' boule, one will note the characteristic "hang" as the bougie is withdrawn.

Treatment. The treatment is gradual dilatation at weekly sessions under local anesthesia until the normal caliber is reached when the intervals may be gradually lengthened. Meatotomy may be necessary in some cases.

URETHRAL CARUNCLE

Caruncle is the most common tumor of the female urethra. It is usually seen in the late fourth or fifth decade of life and is unrelated to previous infection. The cause is obscure. It is a small florid moist, vascular tumor occupying the margin of the urethral orifice. It protrudes from the posterior lip of the meatus and is exquisitely tender not only to touch but upon urination as well. There may be bleeding. The diagnosis is made on histological examination of the removed tissue.

Treatment. Sessile caruncles are destroyed by fulguration. Pedunculated tumors can be excised and their bases coagulated. Spinal or even general anesthesia may be necessary. After any procedure urethral dilatation should always be done.

CYSTOCELE

Many female patients suffering with cystocele will complain of frequency, dribbling and nocturia. Examination will reveal the prolapsed or sagging anterior vaginal wall. The cystocele should be surgically corrected.

PROLAPSE OF THE URETER

Prolapse of the ureter is seen most commonly in young girls and in women over forty years of age. It may be caused by constipation with straining at the stool, violent coughing, prolonged diarrhea, or rape. Some believe the cause to be on a neuromuscular basis. The symptoms are itching, burning, pain and frequency. Inspection will reveal a dark red tumor of variable size protruding at the urinary meatus.

Treatment. Rest in bed and the application of wet compresses are in order. If the prolapse is slight, it may be reducible by manual reduction or by the use of a sound. In more severe cases fulguration or surgical measures may be necessary.

URETHRAL DIVERTICULUM

Urethral diverticulae may be congenital or acquired. In many instances they follow childbirth, particularly a prolonged and difficult delivery. They are usually found in the urethrovaginal wall. There may be recurrent attacks of cystitis and the patient may complain of dysuria, frequency, pyuria and pain on coitus. The *diagnosis* is made by urethroscopy and urethrography. The *treatment* is surgical and consists in the resection of the pouch by the vaginal route.

LEUKOPLAKIA VULVITIS

This condition should always arouse the suspicion of carcinoma. They are best treated surgically for the reason that 25 per cent of cases are followed by malignancy of the vulva. Timely and appropriate use of vitamin and estrogenic therapy may prevent, alleviate or cure these processes. Local applications and radiation have no effect on the intolerable itching that accompanies these lesions.

SENILE VAGINITIS

Atrophy of the vagina in the aged makes it more susceptible to infection and injuries. Infections frequently arise from the site of erosions which may progress to an adhesive or obliterative vaginitis. It may present itself as a thin, reddened vaginal mucous membrane and there may be an associated vulvitis. Itching may be intolerable. The treatment is based upon cleanliness and general nutrition. Lactose tablets with or without citric acid (2 per cent) are beneficial for local use. Almost miraculous results have been reported using 10,000 r.u. of a estradiol benzoate administered intramuscularly at biweekly intervals for three weeks.

MYCOTIC VULVOVAGINITIS

Diabetes is believed to favor the development of a mycotic vulvovaginitis but many clinicians think the term diabetic vulvitis is inaccurate and should not be used. Monilia thrive in an acid sugar medium which is closely

approached in the vagina during pregnancy Many of these patients do not develop symptoms The diagnosis is apparent upon finding white flaky curd like particles in the vaginal secretion and adherent to the vaginal mucous membrane A vaginal smear examined under high dry power will confirm the diagnosis Pruritus vulvae in the presence of an acid vaginal medium mature vaginal smears and the absence of trichomonads should suggest *moniliasis*

Lactic acid douches are prescribed The vagina is painted with half diluted Lugol s solution twice weekly Capsules containing the following prescription are inserted in the vagina each evening

℞ Potassium iodate	0 035
Potassium iodide	0 215
Colloidal neutral kaolin	
q s to fill #24 capsules (gelatin)	
M et F pulvis	
D T S XXIV	

Excellent results have been reported with silver picrate The vagina is cleaned with an aluminum gel kaolin suspension after which it is painted with a 1 per cent aqueous solution of silver picrate crystals After the vagina is dried it is insufflated with a 1 per cent silver picrate powder This is followed for several weeks by daily silver picrate suppositories

TRICHOMONAS VAGINITIS

This is frequently found in the vagina with a pH toward alkalinity In a suspected case the pH is determined with nitrazine paper and after exposing the cervix by means of a dry speculum the os is swabbed with a cotton applicator and the secretions are rinsed into a test tube containing about 3 to 5 c c of *normal salt solution With another swab* the vaginal vault is swabbed and this material is placed in the test tube containing the saline mixture A drop of this material is placed on a *slide under a cover glass and examined under* low power to see the movement of the trichomonads and high power to confirm their morphology

*The treatment is often protected and recur*rence are common Stovarsol medicated tampons are beneficial in the acute phase Other medications are silver picrate insufflations and suppositories floraquin suppositories and insufflation of 2 drams of sulfathiazole powder

PROLAPSE OF THE UTERUS

This is frequently seen in the aged as a result of previous birth trauma It results in relaxation and extreme prolapse of the genitalia accompanied by the bladder and rectum The symptoms are a dragging heavy sensation in *the lower back and some urinary and defeca*tion difficulties Cystitis and constipation is the rule

The treatment is prophylactic by proper repair at the time of and following childbirth Palliative treatment can be accomplished by the fitting of a hard rubber pessary, but these are not satisfactory in all cases as the pelvic floor may be so damaged that it will not retain the pessary

DISEASES OF THE PROSTATE GLAND

The prostate gland is the most important of the accessory male sexual glands It is a musculoglandular organ situated at the neck of the bladder and enclosing within its structure the prostatic portion of the urethra and the ejaculatory ducts It enlarges rapidly at puberty and fails to grow in persons castrated in youth It atrophies in men castrated in adult life The only proven function of the prostate gland is the production of an external secretion which combines with the secretions of the seminal vesicles Cowper s glands the mucous glands of the urethra and the testicular section at the time of ejaculation to form the seminal fluid The prostatic fluid is believed to dilute the testicular and seminal vesicular secretions and activate the spermatozoa

Normal prostatic secretion is opalescent *thin slightly viscid and either alkaline* or neutral Its opalescent appearance is due to the presence of lecithin bodies Corpora amylacea are normally found upon examina*tion of the fluid Other morphological* elements are columnar epithelia in moderate amounts a few erythrocytes and leucocytes and an occasional hyaline globule

It must be stressed that no clinical study of a male patient can be considered complete unless a rectal examination is done There are many misconceptions regarding the examina

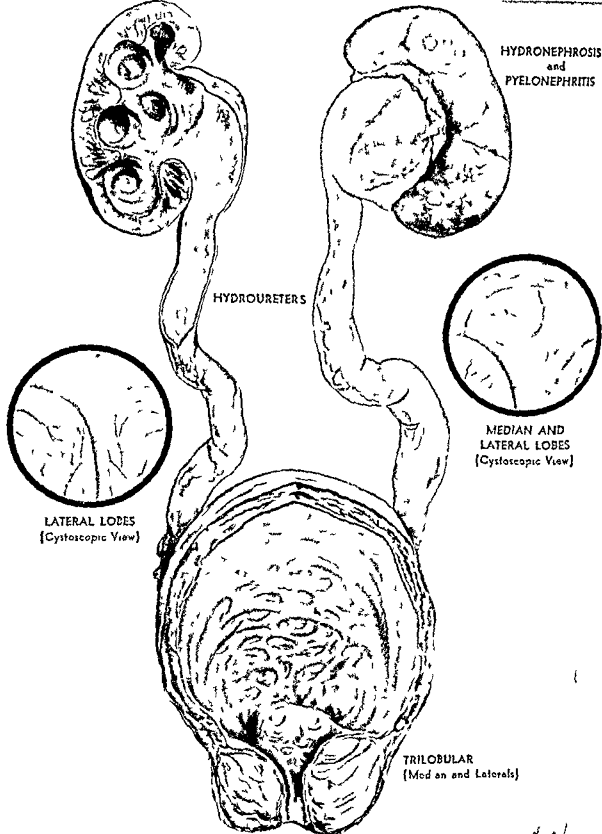


PLATE X (*continued*)
Benign Prostatic Hypertrophy

(*Courtesy Ciba Pharmaceutical Co. Used by permission.*)

should be approached with caution In robust males the bladder can be safely emptied at once In others emptying should be gradual and in those with chronic retention, they should first be put to bed and the bladder decompressed very gradually

The patient should pass all the urine he can voluntarily and preferably in private where others may not distract him He should then be catheterized and the amount of urine recovered carefully measured If residual is found a germicide, non irritating in character should be instilled into the bladder If residual urine is present other causes of residual urine must be excluded (1) neurogenic bladder (2) diverticulated bladder (3) hydronephrotic ureter (4) carcinoma or tuberculosis of the prostate (5) solitary cyst of the prostate and (6) bladder stones or new growths If the patient is a good risk and the diagnosis is in doubt *cystoscopy* is advised It is not a procedure for the amateur and it should be undertaken very guardedly in any patient with an enlarged prostate

Treatment In cases of slight enlargement little or no urinary symptoms or retention the treatment may consist of periodic prostatic massage gentle dilatations of the urethra by sounds urethrovesical irrigations hot sitz baths perineal diathermy and forced fluids In some cases hormonal therapy affords symptomatic relief Periodic check up is an essential part of the treatment of these early cases

The bladder and upper genito urinary tract are not adapted to withstand back pressure for long without suffering irreparable injury If a median bar is the cause of the obstruction transurethral resection is indicated in exaggerated intravesical obstructions suprapubic prostatectomy is indicated perineal prostatectomy is indicated in those cases in which the hypertrophied gland is outside of the bladder The facts should be presented to the patient and he be allowed to make up his own mind as to the disposition These patients are problems for a competent urologist The general practitioner may keep the patient under observation for a period of time to await the possibilities of residual urine but once this has developed the patient should be referred to a competent urologist with operative intervention in mind

In those patients who are poor surgical risks or who for some reason refuse operation hormonal therapy should be considered This does not imply that hormonal treatment can or should be considered a substitute for surgery in major prostatic obstructions Recent reports using *diethylstilbestrol* have shown marked functional improvement as well as actual diminution in the size of the prostate gland These encouraging reports warrant further study and trial of these preparations

Carcinoma of the Prostate Gland

Carcinoma of the prostate gland is present in almost 25 per cent of all men who reach the age of 60 but because of its slow growth a majority of those dying do not die of the disease itself Young s studies reveal that 20 per cent of males seeking relief of obstruction of the vesical neck have carcinoma of the prostate The diagnosis is made in only a few cases early enough to offer any chance of successful treatment The etiology of carcinoma of the prostate is unknown A recent concept suggests a relationship of the androgenic hormone to carcinoma of the prostate Dr Chas Huggins and associates have shown that carcinoma of the prostate is often composed of epithelial cells of a mature type which are responsive to the depression of the level of androgenic hormones in the organism Castration or neutralizing the activity of the gonadal androgens by estrogen therapy decreases the activity of the prostatic carcinoma

Carcinoma usually makes its appearance after forty five years of age and few conditions are more certainly fatal Metastases have usually occurred before the diagnosis is made and roentgen studies will reveal bone changes in the spine or pelvis There are three types (1) *acute fulminating* which leads to a fatal exitus in a few months (2) *disseminating* type in which the growth is small and general metastases are present almost from the beginning and (3) the most common type *scirrhous carcinoma* in which the growth remains localized a long period before dissemination takes place to the viscera and glands Carcinoma of the prostate usually *infiltrates* the posterior aspect of the gland in advanced cases there is an invasion of the posterior urethra triangular ligament seminal vesicles

tion of the prostate gland One cause of error is probably derived from the habit of describing the size of the organs of the body by comparing them with well known objects such as fruits vegetables and marbles We often forget that there are various sizes of grapes, horse chestnuts apples and oranges The prostate is usually compared with a horse chestnut, but if the doctor has not seen a horse chestnut since his boyhood, his memory of its size may be a bit unreliable As a consequence, if the gland is larger than his mental picture of the chestnut the patient is surely thought to have hypertrophy, if it is firm carcinoma is suspected

Prostatic Hypertrophy

Prostatic hypertrophy is by no means a misfortune of the aged alone It has been shown to be present in 2 6 per cent of 112 patients between 20 and 29 years of age It is usually larger in those past fifty, sometimes being twice the size normally seen at twenty years The gland can be enlarged at its vesical or urethral outlet and yet, upon palpation show no sign of enlargement It has been estimated that over 50 per cent of median lobe enlargements in the absence of hypertrophy of the lateral lobes escape detection by rectal examination alone Benign prostatic hypertrophy affects certain areas within theprostate and is not a diffuse hyperplasia of the entire organ The portion which hypertrophies most frequently is that portion adjacent to the urethra There are several types of gross enlargement recognized (1) bilobular (two lateral lobes (2) trilobular (two laterals with median) (3) unilobular (median) and (4) circular or confluent enlargement at the vesical orifice The configuration of the lobes is readily recognized by cystoscopic visualization Obstruction to the posterior urethra results in changes in the bladder ureters and kidney Voiding requires increased pressure which leads to hypertrophy and thickening of the bladder wall which when the limit of hypertrophy is reached a gradual decompensation and dilatation results with the development of a residual urine The obstruction may progress to the point where the back pressure is transmitted to the ureters and kidneys producing a dilatation of the ureter and a hydronephrosis If the obstruction is not relieved, there is a progressive decrease in renal function, frequently resulting in uremia and death

The *shape* of the prostate gland varies considerably It can be flat on its posterior surface, and may extend superolaterally under the seminal vesicles The *consistency* of the prostate gland also varies It may be firm suggestive of a carcinomatous prostate in normal individuals Nodules palpated may be of inflammatory origin, but in the vast majority of cases, they suggest carcinoma or tuberculosis *A nodular gland should never be massaged until these two conditions are absolutely ruled out*

Symptoms and Signs 1 Troublesome nocturia, frequency slowness of the stream which lacks propulsive force, and dribbling toward the end of micturition

2 Retention may be induced by exposure to cold, dampness alcoholic overindulgence, or other irritative factors

3 Pain may be present if the residual urine is great in amount

4 The early stages may be associated with an increased libido, and increased erections in the later stages there is loss or diminution of libido

5 Obstruction, renal decompensation and toxemia may follow An increased blood urea nitrogen is a grave sign

6 After infection sets in the urine may contain considerable pus blood and albumin

Diagnosis The patient must be given a thorough general and special examination including rectal palpation an estimation of the amount of residual urine renal function determinations and a cystoscopic examination to evaluate the nature of the enlargement As to the diagnosis by rectal palpation much depends upon the experience of the examiner The size of the prostate is no indication of its potential obstructiveness Conversely a gland seemingly of normal size does not rule out obstruction of the neck of the bladder by a median bar or hypertrophy of the subcervical group of tubules Lowsley and Kirwin point out that the extent of intravesical and intraurethral intrusion can only be determined by cystoscopy cystourethrography or suprapubic cystostomy When retention is suspected it

proper approach to therapy If metastases can be excluded an attempt can be made to eradicate the disease by perineal prostatectomy If metastases are present hormonal therapy or transurethral resection are in order Also the test is of aid in establishing whether existing metastases are of prostatic or non prostatic in origin and as an index to recurrence following the surgical removal of the gland or to the spread of metastases

Treatment Surgical removal remains the ideal treatment for carcinoma of the prostate gland Other methods are radiotherapy by radium or deep x ray hormonal therapy which may take the form of castration, irradiation of the testicles or the administration of testosterone propionate or diethyl stilbestrol If the disease is too extensive for radical extirpation some advise irradiation by means of radium needles or radon seeds or surface application of radium and deep x ray therapy to the prostate as well as known metastatic sites Castration the newest method of treatment has shown striking improvement in the clinical condition of patients with advanced metastatic prostatic carcinoma For those who refuse castration or who are poor operative risks, stilbestrol can be given orally in doses ranging from 1 mgm weekly to 3 mgm daily or it can be implanted under the skin in pellets

Focal Infective Prostatitis

This is a disease of later years between fifty and sixty years of age In almost all cases it is secondary to foci in the teeth tonsils and more rarely in the gall bladder The treatment consists in gentle massage of the gland at three or four day intervals the progress being carefully followed by a microscopic study of the secretions If there is no change in six weeks the patient should be restudied for oral infections, and if still no improvement is seen after four months of treatment a two month period of rest is advised Any excess over six polymorphonuclear leucocytes in the prostatic secretion is regarded as evidence of infection

Pelouze (8) has warned that we should no longer plunge blindly along in our treatment of the prostate gland as has been the custom heretofore as the damage that may follow such procedures is far too great to be viewed lightly This is particularly true of lesions of the heart and the eye in which the prostatic infection plays a casual part since both these organs may suffer irreparable damage by any procedure that forces into the system a larger dose of the offending toxins present that the tissues can stand For this reason one should think of massage more from the viewpoint of toxin dosage than from that of prostatic drainage The contraindications to prostatic massage are stated on page 1168

Treatment In addition to massage mentioned before other measures such as the application of heat in the form of perineal diathermy hot sitz baths or hot rectal irrigations sedatives and suppositories for pain and forced fluids by mouth if there is no retention

Chronic Prostatitis

Chronic prostatitis is frequent in adult males it is often the end result of the acute stage or, it may be secondary to focal infection By no means are all cases due to gonococcal infection The prostate gland is an important focus of infection and is regarded by many urologists as being second only to infected tonsils as a cause of arthritis It may also be responsible for bursitis iritis myositis neuritis and endocarditis The acini of the gland contains pus cells and the surrounding stroma is infiltrated with round cells and leucocytes Varying degrees of fibrosis is present throughout the gland The gland may feel normal on palpation and so rectal palpation in itself is not sufficient to establish the diagnosis The symptoms and signs vary greatly Pain is often referred to the back perineum testicles thighs and scrotum There may be nothing more than a morning drop ' or there may be burning and frequency urgency difficulty pyuria hematuria and dribbling as well as loss of libido weak erections bloody painful ejaculations nocturnal emissions and a sense of heaviness in the rectum The predominant symptom may be metastatic such as those associated with arthritis iritis neuritis or myositis The *diagnosis* is confirmed by rectal palpation repeated studies of the urine microscopic study of prostatic secretions and in the hands of one experienced in the procedure a urethroscopic examination of the posterior urethra and bladder neck Methods of securing the specimen of prostatic secretion has been discussed el e

and at times an extension into the bladder, peritoneum, and rectum The gland is richly endowed with lymphatics through which carcinoma is spread to the pelvic nodes or by the perirectal plexus to the abdominal nodes Dissemination through the blood stream may occur early

Symptoms Prostatic carcinoma is a silent painless lesion until either obstruction, bladder invasion, or metastasis occurs Benign hypertrophy may be present and the symptoms are much like those of simple hypertrophy frequency, nocturia, difficulty in starting the stream, and dribbling The symptoms which bring the patient to the physician are usually urinary retention and hematuria though there may be pain noted in the sacro iliac region penis rectum perineum or thighs Late symptoms are loss of weight, anorexia and loss of strength

Diagnosis As a rule the diagnosis is made on the history rectal findings and study of a biopsy specimen A carcinomatous prostate is hard board like unyielding tense fixed and nodular or irregular in contour There may be only microscopic malignant areas in a gland that is macroscopically benign Diagnosis may be very difficult in the soft medullary type or in that superimposed upon a benign hyperplasia It should be suspected in all cases of dysuria, frequency and retention in males of the cancer age *Roentgen study* may show metastases in the pelvic and other bones When rectal palpation is suspicious a *biopsy* specimen should be examined This is best done by surgical exposure of the gland through the perineum with excision of a piece of tissue from the suspected area The *laboratory* may be of assistance since it has been shown that the serum acid phosphatase will be markedly elevated only in prostatic carcinoma with metastases to bone and far advanced osteitis deformans A differential point between these two is that in osteitis deformans high readings of serum alkaline phosphatase are found and the roentgen findings are characteristic While the serum alkaline phosphatase may be elevated in prostatic carcinoma the levels are never as high as those noted in osteitis deformans As shown by Curtis (1943) in the U S Naval Bulletin the serum acid phosphatase test definitely establishes the diagnosis of carcinoma of the prostate gland with bone metastases and it is an aid in selecting the

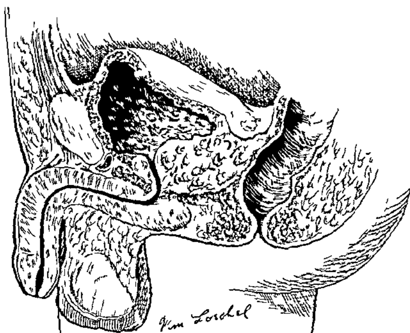


FIG 225 Carcinoma of the Prostate Gland Showing Extension into the Bladder Peritoneum and Rectal Wall

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where The *treatment* consists in prostatic massage, dilatation of the prostatic urethra, heat applied in the form of hot sitz baths, diathermy or rectal irrigations and chemotherapy Hyperpyrexia is of great benefit in selected cases but should be given only in a hospital staffed with trained personnel acquainted with its complications Rarely when no treatment is of avail prostatectomy is indicated

Prostatic Abscess

Suppuration during acute prostatitis may result in the formation of an abscess abscess may also follow failure of the acute process to subside or become chronic abscesses may result from too enthusiastic instrumentation prostatic abscess may occur as a complication of typhoid fever influenza diabetes mellitus septicemia or pyemia lastly they may be secondary to pyogenic infections Abscesses

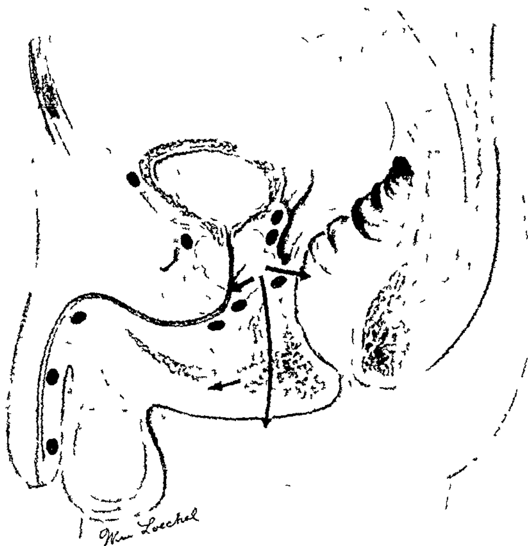


FIG 226 Arrows point to routes of rupture of a prostatic abscess Circular areas represent the areas of abscesses following acute gonococcic infection

following gonorrhea are usually not as severe as those following or due to a pyogenic infection If untreated the abscess may extend through the prostatic capsule in several directions, into the rectum or upward into the cul de sac resulting in peritonitis It may also rupture into the urethra The *symptoms* are perineal pain chills painful urination which may progress to complete retention and fever The gland may be large and asymmetrical upon palpation as well as tender and fluctuant The *diagnosis* may be made by the history, the physical examination and cysto urethrography A needle may be inserted into a suspected portion of the gland and pus withdrawn if present

Treatment Non gonorrheal submucosal abscesses associated with cystitis are treated with heat in the form of hot sitz baths diathermy and sedation When the frequency has subsided potassium permanganate irrigations (1 8000) are prescribed followed by gentle prostatic massage Where no cystitis is present, irrigations may be instituted immediately but the massage should be delayed for about two weeks It is well to give sulfadiazine or sulfathiazole to these cases Large abscesses may break through the gland capsule and involve the periprostatic tissues in which case after a few days of sulfadiazine or sulfathiazole therapy incision and drainage through the perineum should be done

HYDRONEPHROSIS

Hydronephrosis may present itself in the aged particularly after the sixth decade It may be bilateral Causes are lesions of the bladder neck carcinoma calculi and contracture of the neck of the bladder ureteral kinks and prostatic hypertrophy Hydronephrosis is more common in the aged male than the aged female For more complete discussion see page 345

PEYRONIE S DISEASE (PLASTIC INDURATION)

This is a disease of unknown cause characterized by the occurrence of fibrosis of the sheath or septum of the corpora cavernosa extending into the tunica albuginea The plaques grow in the axis of the organ causing a curvature which interferes with coitus The penis may be flail like the terminal segment being flaccid while the proximal portion is erect This is a disease of early senility, though it may occur in the third or fourth decade The treatment is very disappointing, and surgery usually makes the condition worse Roentgen therapy has been helpful in a few cases but the patient should not be promised a cure

CARCINOMA OF THE PENIS

Carcinoma (epithelioma) is the most common malignant tumor of the penis but comprises less than 1 per cent of all neoplasms In the U S Marine Hospital Service, 7 cases have been reported among 70 826 patients It is usually painless until late in the course of the disease The majority of cases are seen between the ages of forty and sixty years of age The growth is a typical warty epithelioma which rarely extends into the cavernous tissue Metastases occur early by way of the lymphatics to the inguinal nodes but visceral metastases are unusual

The clinical diagnosis of early penile carcinoma is very difficult as the leson may resemble a simple exuberant wart, a syphilide chancroid or a tuberculous lesion In the event of all the clinical diagnostic tests being negative it will be necessary to secure a specimen for biopsy from the basal area at the point of greatest induration

Treatment Prophylaxis consists in early circumcision the removal of keratoses and other forms of chronic irritation Early tumors may be cured by partial resection following irradiation At any rate this is a problem for a competent urologist and should brook no dallying by the general practitioner

MANAGEMENT OF ACUTE URINARY RETENTION

The most common causes of acute urinary retention in the aged are

1 Urethral stricture
2 Benign prostatic hypertrophy
3 Carcinoma of the prostate gland (See page 1069)
4 Sarcoma of the prostate gland
5 Tuberculosis of the prostate gland
6 Neurogenic bladder
7 Focal infective prostatitis (See page 1071)
8 Bladder growths

9 Posterior urethral tumors
10 Polyps
11 Cysts
12 Foreign bodies in the bladder
13 Following pelvic operations
14 Pressure from external masses

When confronted with acute urinary retention in females one should consider the following causes (1) urethral stricture (2) vesical neck obstruction (3) pedunculated bladder tumors, (4) neurogenic bladder and (5) uterine fibroids, which incidentally, are the most common cause

Urethral Stricture

There is usually a history of a previous urethral inflammation gonorrheal or otherwise There may have been recent trauma to the urethra, as from a straddle injury

Symptoms The symptoms are usually backache, dribbling of urine with difficulty in starting the stream, a slowing of the stream and a chronic urethral discharge

Findings Examination reveals an inflammatory stricture in the urethra or a traumatic stricture in the membranous or bulbous urertha either of which does not permit the passage of catheters or sounds A rectal examination reveals an irregularly firm set of seminal vesicles and prostate

Treatment When a stricture is present small caliber filiforms or catheters should be passed by cork screw like turns thus avoiding any blind pockets that may be present A filiform bougie strapped in the urethra for twenty four hours will permit the trickling of a sufficient quantity of urine along its sides to relieve the patient then a fairly large sound can be passed with ease A LaForte follower may be used but one should be sure that the threads are not worn otherwise one may have difficulty in extricating it from the bladder If it is not possible to first pass a filiform bougie retention can sometimes be relieved by the use of morphine and a hot sitz bath Morphine allays the pain and the heat tends to relax the stricture The patient should be told to try and urinate as he sits in the hot bath

When there is full distension of the bladder one must always think of the patient's cardiovascular condition because of the sudden drop in blood pressure which may follow the sudden relief of tension and also of the possibility of intravesical bleeding It is doubtful whether dilatation will give a permanent cure because there is a tendency for the tissues to contract again It is advisable that these patients have

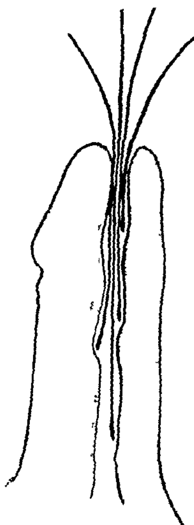


Fig 227 Method of passing multiple filiforms to locate the urethral lumen

their urethral calibers examined at least once a year If dilatation does not cause bleeding it can be done every other day and after a comfortable size has been attained the interval can be lengthened If bleeding occurs the next treatment should be postponed The calibers of the sounds are increased each time by two sizes French if the stricture is resistant or if bleeding results the sound should be decreased

by one size When the sounds are less than No 20 French, only flexible instruments should be used, above this caliber rigid dilators should be employed Dilatation is carried to the point where the penile urethra is put on the stretch Once this has been attained, sounds should be passed once a week for two weeks and again a month later and if there is no sign of recontraction at six month intervals for a year or longer

The prognosis in negroes is unfavorable since they do not cooperate in treatment which they rarely continue with long enough to ensure effective dilatation In such persons it is therefore better to carry out a urethrotomy the results of which last much longer than do the lesser grades of dilatation As a rule the symptoms are not bothersome to negroes as long as they can urinate at all Consequently they are usually acute emergencies when seen by the physician

Benign Hypertrophy of the Prostate Gland

This diagnosis will not be difficult as usually there will be a history of previous attacks of acute retention and of symptoms that accompany prostatic hypertrophy In prostatic obstruction, effective entry into the bladder is secured by using a semi rigid curved catheter with a Coude tip A semi rigid stylet inserted into a Foley catheter is kept in place without adhesive tape Undue force is unwarranted since extravasation of urine may result and bring about another emergency which calls for immediate operation involving multiple bold incisions into the extravasated area Suprapubic cystotomy or trocar suprapubic puncture by the inexperienced is not warranted Spontaneous rupture of the bladder does not occur It should be borne in mind that not infrequently hemorrhage, shock and anuria may result from the sudden removal of urine Therefore gradual decompression of the bladder should be practiced The removal of blood clots blocking the eye of the catheter is best managed not by attempting sucking them into the lumen of the catheter but by forcing fluids through it This is accomplished by attaching a syringe full of fluid to the catheter Only by the use of a metal catheter which will not collapse is it feasible to clear a bladder filled with clots by means of suction

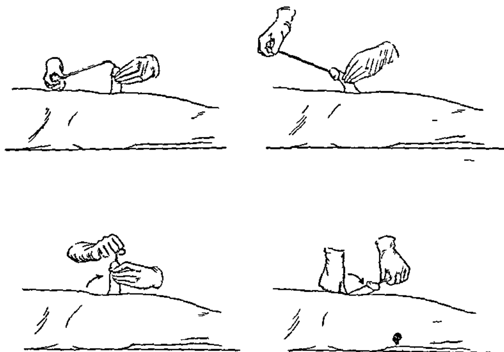


Fig 228 Method of passing a sound

Prostatic Sarcomas

Prostatic sarcomas are rare and the prognosis is very grave As a rule it usually occurs in younger people Weakness and loss of weight may be prominent symptoms Radium and x ray offer only palliative relief

Urinary Retention of Neurogenic Origin

The neurogenic bladder may occur early in tabes myelitis multiple sclerosis and in blood dyscrasias There are three available methods of treatment, namely (1) the bladder is permitted to become overdistended overflow incontinence and urination by the reflex action then resulting Morphine and hyoscine must be given to relieve the pain of overdistension until overflow commences which usually takes two or three days (2) Intermittent or continuous drainage by catheter This usually results in a permanent indwelling catheter and is more successful in the female than in the male (3) Suprapubic cystotomy is the procedure of choice when the condition is expected to be of long duration The operation is not without shock in itself and should never be performed if a state of shock already exists Instead the patient should be catheterized until he is in a better condition Some urologists consider it good practice to give 1 gram of *sulfathiazole* ten minutes before catheterization as when taken orally, it is quickly absorbed

Retention Following Pelvic Operation

The use of prostigmine 25 mgm by hypodermic injection has been disappointing It is better to catheterize often without irrigation

Bladder Growths

Bladder growths causing acute urinary retention usually give a history of intermittent hematuria Cystoscopy confirms the diagnosis

Posterior Urethral Tumors—Polyps—or Cysts

The diagnosis is easily made by urethrocystoscopy or by taking urethro cystograms

Foreign Bodies in the Bladder

There may be true bladder stones Foreign bodies usually occur in younger individuals sex perverts who insert gum beads or hairpins into the bladder

Pressure from External Masses

In this group may be included perivesical abscesses appendiceal abscesses, diverticula of the colon and carcinoma of the bowel

HEMATURIA

Hematuria can occur at any age, but in the aged patient in the presence of hematuria the following conditions must be considered

a Stones
b Trauma
c Benign tumors
d Malignancy
e Nephritis
f Hypertension
g Essential hematuria
h Tuberculosis
i Pyelitis
j Pyelonephritis
k Polycystic kidney

Case Study Methods

This symptom should be investigated by the following means

1 The source of the bleeding should be sought with the cystoscope
2 If from a lesion in the bladder, a large catheter should be inserted, the bladder drained and washed out repeatedly with warm boric solution A retention catheter is then inserted
3 Fulguration may be necessary Obtain tissue for microscopic study if possible
4 Examine the prostate and the urethra
5 Culture the urine
6 Intravenous urography is of value
7 Roentgen study of the K U B tract

RENAL AND URETERAL CALCULI

These are not uncommon in the aged As a rule the presence of bilateral calculi in the kidneys contraindicates surgical removal However, if the symptoms are of such a nature as to warrant operation unilateral stones should be removed For a more complete discussion see page 346

SULFONAMIDE LITHIASIS

Complete obstruction with anuria has been reported following the administration of the sulfonamide drugs The symptoms of renal colic and hematuria in one using these drugs should make one suspicious of crystalline concretions in the urinary tract Roentgen study is of no help as the crystals are not opaque to the roentgen rays

Treatment Fluids should be forced the drug discontinued and 10 per cent glucose administered intravenously If these measures fail one should not delay in seeking urological consultation The usual procedure will be the insertion of catheters cystoscopically into the ureters and pelves of the kidneys in order to lavage them with warm normal saline or sterile water

RECUMBENT LITHIASIS

This may follow lengthy periods in bed It is an emergency and calls for a bilateral nephrostomy immediately when recognized A flat film will differentiate the lithiasis from nephritis since these stones are always phosphatic The treatment is prophylactic—old patients should not be permitted to lie abed for long periods without moving When possible, they should be permitted to sit up in a chair

USEFUL DRUGS IN UROLOGIC PRACTICE AND LOCAL MEDICATION OF THE GENITO URINARY TRACT

With the advent of the sulfonamides and penicillin anterior and posterior irrigations with various solutions such as those listed below are practiced much less frequently than heretofore and are indeed in some instances a thing of the past

Potassium Permanganate Solution of from 1 8000 to 1 3000 are excellent for cleansing mucous membranes as well as being soothing to *vesical inflammation* in the proper strength and particularly to *urethrotrigonitis* Strengths of 1 1000 can be used to remove foul secretions of chancroidal ulcerations on the skin surface They may cause transient pain Such strength should never be used for lavage or topical applications

Silver Nitrate Any portion of the genito urinary tract may be irrigated safely with silver nitrate in strengths of from 1 10 000 to 1 3000 Its use is limited to the instillation of a small quantity into the bladder or kidney pelvis or the direct application to restricted portions of the genito urinary tract such as by local deposition of a 2 or 3 per cent solution into the posterior part of the bladder where it is tolerated well and has a pronounced curative value *It should never be injected into a tuberculous bladder* Its greatest field of usefulness is the topical application on cotton applicators through the endoscope to the posterior urethra

Mild Protein Silver U S P In subacute and acute infections the solution should never exceed 5 per cent and as a rule most patients do better on a 2 or 3 per cent solution The solution will exert a greater effect if the mucous membranes are first cleansed by the use of 1 8000 potassium permanganate When this solution is used for the anterior urethra it should be held there for ten minutes When it is used in the bladder it should be retained until the next act of micturition

Strong Protein Silver This preparation should never be used routinely any stronger than 0 5 per cent as it both produces and sustains a urethral discharge It has been recommended by some for the treatment of anterior gonorrheal urethritis in solutions weaker than 1 per cent

Neosilvol This is sometimes used in *non gonorrheal anterior urethritis* It is used in from 5 to 10 per cent solution it is non staining

Neutral Acriflavine This solution in a strength of 1 4000 to 1 3000 is used as a preventive of infection from instrumentation being injected through the urethra and left in the bladder after cystoscopy It is specific for trichomonas vaginalis infestation of the urethra in a strength of 1 3000

Boric Acid In the presence of cystitis boric acid exerts a soothing effect upon the bladder In a 5 per cent solution it is a useful detergent and is also useful in the removal of blood clots from the bladder

Bichloride of Mercury 1 20 000 is sometimes used in tuberculous bladders

Oil of Gomenol This is useful in *inflamed bladders* when injected in 20 per cent strength by bulb syringe or by catheter It is of value in the *tuberculous bladder* and in the intolerant

bladder following prolonged cystoscopy as well as after fulguration of a panmural cystitis One ounce is instilled and allowed to remain as long as possible *Guaiacol with calomel* is however a better preparation Its formulae is

Liquid guiacol 3 per cent
Calomel 5 per cent in olive oil

Acetic Acid This is used in the *removal of venereal warts* A mixture of salicylic acid 4 gm and glacial acetic acid 30 c c is applied to the warts until they are covered and then allowed to dry It is applied carefully, and any excess mopped away As a rule the growths will disappear in a day or two

Carbolfuschin This is of benefit for the relief of pain and healing in *chancroid ulcers* It is alternated with 1 per cent solution of gentian violet for a few days and then applied again

Zinc Salts The following prescription has been of great use in the treatment of non specific urethral discharges of unknown etiology which fail to clear up on other medication It is not to be used in the treatment of gonorrhea

℞ Zinc sulfate	
Lead subacetate aa	0 75
Camphor water	45 0
Distilled water q s	192 0

Sodium Bromide

Uses A mild sedative for slightly nervous patients or hypnotic for the apprehensive patient

Dose Five to 30 grains in tablet form or with liquid Discontinue at the sign of toxic symptoms

Acetylsalicylic Acid

Uses In lesser grades of local pain in muscle ache of fatigue, *for nocturia and frequency* (gr X at bedtime) The judicious use of aspirin avoids resorting to opiates

Dose Grains 5 q 4 hours or grains 10 at bedtime If accompanied by severe pain add 5 grains of acetphenetidin

Barbiturates The barbiturates have a prolonged effect which *is often desirable in urologic patients* especially in those bed ridden with indwelling catheters Dose Barbital grains 2 to 5

Belladonna

Uses Allays vesical spasm and discomfort, of questionable benefit for eneuresis in children

Dose Tincture of belladonna—5 to 20 minims

Calcreose

Uses Sedation of the nerve endings in bladder inflammations early gonorrheal urethrotrigonitis and for nocturnal discomfort and frequency accompanying obstructions to the vesical outlet

Dose Grains 8 to 16 one hour after meals and upon retiring The drug can be taken over prolonged periods without harm

Depropanex (Sharpe & Dohme)

Uses Renal colic

Dose 3 c c intramuscularly It can be repeated several times in the 24 hour period

Diluted Nitrohydrochloric Acid

Uses Urinary acidulant

Dose 1 to 2 c c diluted with one half glass of water every four hours

Hyoscyamus

Uses Vesical spasm and discomfort eneuresis in children Has a profound action on the peripheral nerve endings

Dose 20 to 30 minims of the tincture

Paregoric

Uses Bladder discomfort, tenesmus and nocturnal frequency

Dose 1 dram before retiring

Potassium Acetate

Uses To shift the pH of the urine to the alkaline side and thus increase diuresis

Dosage In solution 0 5 to 2 5 grams

Suppositories

Uses Marked frequency burning bladder tenesmus nervous sexual symptoms in chronic prostatitis

Formulae

Icthyol	3 0
Extract of belladonna	0 03
Potassium iodide	0 30

Mersalyl U S P (Salyrgan)

Uses A diuretic in edema of cardiac origin

Dose Available in 10 per cent sterile solution, plain and with theophylline First day 0 5 c c intravenously or intramuscularly Second day 1 c c by the same routes For best results ammonium chloride should precede this drug for two or three consecutive days

Mercupurin Action and uses similar to mersalyl

Dose Ampules of 1 or 2 c c of 10 per cent solution can be given intramuscularly or intravenously

Potassium Nitrate U S P

Uses Diuretic

Dose Enteric coated capsules 0 5 gm Daily dose 5 grams

Theobromine N N R

Uses This drug is employed in cardiovascular insufficiency and as a diuretic The forms used are theobromine sodium salicylate (diuretin) and theobromine sodium acetate

Dose Theobromine sodium salicylate—0 5 to 1 0 gm three times daily

Theobromine sodium acetate—0 25 to 0 6 gm three times daily

Methenamine U S P This is useful in infections of the genitourinary tract providing the urine is acid or can be rendered so by an acidulant such as sodium biphosphate It decomposes into formaldehyde in an acid medium The patient must retain his urine so it is of little value in those with frequency or incontinence It is contraindicated in acute bladder inflammations It should be discontinued if any hematuria results It is useless in infections at kidney level and it should be given with a reduced or normal fluid intake

Dose Tablets 0 3 and 0 5 gm Daily dosage is 0 3 to 1 0 grams three times daily dissolved in water

Phenol U S P Liquified phenol in 1 40 1 60 or 1 80 dilutions is useful in the treatment of tuberculous cystitis Bladder instillations must be carried out by means of a catheter to protect the urethral mucosa

Mecholyl

Uses This is useful in cases of residual urine from the loss of contractile power and in difficult urination resulting from faulty muscle contraction

Dose Mecholyl bromide (tablets 0 2 gm) 200 to 300 mg daily by mouth

Mecholyl chloride 20 to 25 mg subcutaneously for prompt action

Sulfonamides See chart on page 1039

Antuitrin S

Uses The gonadotropic action of this drug is used in the treatment of cryptorchidism

Dose 300 to 1500 units weekly for 3 weeks

Stilbestrol This is a synthetic crystalline estrogen used in the treatment of benign prostatic hypertrophy and in carcinoma of the prostate gland It is used to counteract the symptomatic effects of castration

Dose 1 mg daily orally or intramuscularly

Testosterone

Uses Testosterone is used in the treatment of cryptorchidism, hypogonadism and to counteract the effects of castration in the male

Dose 10 to 25 mg injected intramuscularly in oil daily

THE USE OF HEAT AND COLD IN UROLOGIC PRACTICE

Heat is very useful in epididymitis vesical discomfort or inflammation and in acute prostatic inflammation Heat should not be continued too long It should be removed for one hour several times during the twenty four hour period Some patients get more relief from an ice bag thus one should change to cold when heat gives no relief

Hot Sitz Baths

The hot sitz bath for some reason does not receive the attention due it It is of great value in *acute retention of urine* It should be tried whenever possible before resorting to the catheter It should be used with caution if at all in those with *cardiovascular disease* They should be advised to leave the bath at the first sign of dizziness faintness or weakness It is

used by many as the sole treatment in vulvovaginitis, and some believe the cure of gonorrhea is hastened by employing sitz baths with other treatment

Technique The patient sits in water reaching to the iliac crests with the temperature maintained just below the skin tolerance by the frequent addition of more hot or cold water as desired The patient should stay in the bath for from 20 to 30 minutes and baths should be repeated about 4 or 5 times daily When no sitz bath is available, the patient can roll up a turkish towel, and after soaking it in hot water, place it between his legs against his perineum and sit on the shower room floor

Rectal Heat

Rectal heat applied to the prostate gland reduces inflammation and congestive swelling as well as subjective symptoms and, it prevents some infected glands from going on to abscess formation The gland temperature is not greatly elevated in so called prostatic diathermy Hot rectal lavages are the safest means of applying heat to the subvesical structures in the presence of infective swellings

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Chapter XX

THE CARE OF THE AMBULATORY PATIENT

In modern hospital and clinical work it is becoming more and more difficult to practice the art of medicine The busy routine of the clinic does not lend itself readily to a painstaking and broad consideration of the patient as an individual as well as of his disease It is time consuming to listen to a long story about the home situation which at the time seems irrelevant yet often during such a recital the true cause of a patient s illness is discovered It is in the hurried busy life of a large institution, clinic or dispensary, that the young doctor, particularly, may unconsciously acquire habits which will militate against his future success The hurried business like approach to the patient—the thorough orderly, systematic, quick but frigid examination of some frightened patient may give that patient an unfortunate impression of the institution and its doctors Even in the ward of tho e hospitals where all the physicians are closely associated it sometimes happens that not one of them becomes the patient s personal adviser, coordinates the efforts that are made in his behalf and sees to it that his emotional as well as his physical problems receive their due share of attention

In spite of the improvement in medical facilities the great mass of the population is not yet receiving the good medical care that the medical profession is capable of giving Statistics concerning the supply and distribution of physicians and the number of potential patients within their reach in the country at large vary greatly but are of little if any value since they do not indicate the type of care available to the patient The true situation is better shown by the number of patients who come to hospitals with an unrecognized and hopeless cancerous lesion a neglected and advanced pulmonary tuberculosis or a long standing severe but preventable type of infection Too often one finds that the doctor who has first seen the patient failed to make even a cursory physical examination a rectal examination palpation of the breast a careful study of the chest, or a blood count or urinalysis Without being unfair to the medical profession we must admit if we face the facts either that the general population has not been made sufficiently public health conscious that many of our general practitioners are incompetent to render adequate medical care or that the present system of practice does not permit them to render the service of which they are capable

From the viewpoint of the hospital s service to the community the outpatient department may become and perhaps already is of greater importance than the ward A larger number of patients can be cared for in most instances in the earlier stages of their disease and more can be cured and made useful citizens In addition many of the patients if it were not for outpatient service eventually would become ward patients and as such require the additional expense of lodging supplies and board Furthermore, many outpatients even while under observation may continue their employment and continue as productive citizens Therefore it is wise and economical for the hospital as a public institution to contribute to outpatients all its available resources for diagnosis and treatment

In some institutions only the younger and less experienced clinicians do the outpatient work, but from the viewpoint of their service to the community the more experienced staff members if only in an administrative or consultant capacity would be of greater value in the dispensary than on the ward It is to be hoped that these experienced men after many years of contact with the type of patients seen in outpatient practice do not become too hard boiled and free in their diagnosis of gold brick or neurotic The doctor is apt to forget that the beginnings of disease are insidious cause little disturbance of function and often give no detectable signs Sooner or later they lead to symptoms and the patient first seeks medical advice at a time when the most careful medical examination will often

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understanding and of an obvious desire to help It rarely requires any extra time to develop such a relationship for it is largely a matter of the physician s manner and of his consideration of the patient's personal as well as of his specific medical problems The interest must be maintained however and must extend to the patient's management so long as he is under the physician s observation

The study of the patient should be intelligently complete and not needlessly comprehensive If every known examination were made of every patient much that goes undiscovered in diagnosis might be disclosed but who could survive the physical and the psychic ordeal trauma, or the financial strain? The routine performance of needless tests indicate a lack of skillful observation and thinking dulls clinical acumen and wastes time and material

Patients who have an acute or a self limited disease should be given an approximate estimate of when they will recover and when they will be able to resume their usual activities for such information will be a comfort to them but with those whose period of illness is indeterminate *one should not guess* If one states the likely length of incapacity and it proves to be shorter than promised it may be a gratification whereas if it be longer than was forecast there will be disappointment even depression In many cases in order to gain the full cooperation of the patient he must be told the exact nature of the disease and its gravity If he has a disease that demands rest, will he abandon his career to secure it when he has been assured that he has no serious physical fault?

Instructions to the Patients

A a safeguard against misunderstandings the doctor should follow the practice of giving his patient printed instructions rather than depending upon oral instructions This also saves the time which otherwise the patient would spend in making repeated inquiries regarding details Written instructions also preclude the possibility of the doctor failing to remember oral instructions previously given Written instructions carry more weight with patients many of whom have probably at one time or another received them from well organized clinics or hospitals Some states actually require the doctor to supply a patient suffering with a venereal disease a circular of information and advice The instructions can be mimeographed and additional space can be left for additional or modified directions as well as the date name and address of the patient At the conclusions of the instructions it is well to add the following

> If there is anything that is not clear in the above directions make a list of your questions in the space provided below so that they may be answered at your next visit

Report for treatment on

The following instructions some of which are used at the Peter Bent Brigham Hospital Boston Mass are representative of the type of instructions used in the larger clinics in this country

MANAGEMENT OF ACNE

You are suffering from a skin condition which is not uncommon at the period of puberty and during early childhood It is somewhat resistant to treatment and not infrequently has a tendency to recur after apparent cure However there is no cause for worry Do not expect a cure in a few treatments It usually takes time for a definite sign of improvement to appear Do not discontinue treatment before you are discharged by me

You will assist materially in affecting your cure if you carefully follow the instructions listed below Disregard any other advice which you may receive it will only tend to confuse you

1 Get plenty of sunlight fresh air and exercise
2 Get plenty of sleep—at least eight hours a night
3 *Diet* Avoid an excess of starches and sweets particularly candy pastry etc Eat a moderate amount of rye bread and avoid white bread Eat as little fish and shell food as possible You may eat plenty of vegetables except potatoes Eat other foods that give you the necessary vitamins such as fruits cereals

fail to reveal any objective cause for his discomfort How little many of them are understood and how often they are misinterpreted! Who among physicians has not labeled such a complainer without abnormal signs a hypochondriac a neurotic or even a malingerer, only to be embarrassed later to find that disease has developed and made him ready to subscribe to the saying of the late Wm S Thayer, 'After twenty years I relabel my neurotics, my diagnostic errors

We should never take another s word for a diagnosis A neurotic is neither malingering nor is he hysterical This is the last diagnosis one should make, as it is an exclusion diagnosis *and therefore particularly dangerous* Once the word neurasthenia" or neurosis' gets on the patient's health record he ceases to be of interest to most members of our profession If he should actually have or should develop later any organic disease, it is apt not to be recognized as such for a long time In addition, should the patient be a seaman or a member of the armed services it is not unlikely that some of his superiors will see some of his health record or the papers relating to his treatment, and it is surprising how the word will be passed around that so and so is a nut ' The writer has seen many examples of this, one in particular which led the patient to an attempt to take his own life

There are many people with functional disorders Functional disease is widespread and is increasing at a rapid rate The present world situation with its relative insecurity of the future is more than many can stand We must remember that nearly all our patients with organic disease are emotionally disturbed at the time of the first examination and because of this it is of very great importance to decide whether it is wise or best to concentrate our efforts alone on the organic lesion or to treat the patient in a broad general way provided that there is no danger in delay Many patients are accepted for operation in good faith and are thought to be well after the wound has healed They are listed as cured and sent to the outpatient department having returned home or to work in a troubled environment which may have been largely responsible for their illness They then present a problem to the outpatient physician and often to the psychiatrist who may have reason to doubt the efficacy of the surgical treatment

It is astonishing to what extent the development of efficient outpatient departments, in addition to the advance in methods of therapy, has diminished the reference of certain patients to hospital wards Not so many years ago, our wards were filled with patients of a type that are now equally or better treated on an ambulatory basis, especially those with diabetes, pernicious anemia, peptic ulcer and gall bladder disease, and some with cardiac, renal and pulmonary disease Now such patients rarely need be admitted to a hospital for diagnosis and for treatment only when the *disease is well advanced or refractory or* demands prolonged rest in bed or surgical treatment

The chief difficulty in the outpatient department concerns one of the essentials of good medical care, namely, the continuous personal supervision of the patient This, however is because we have not always given proper consideration to the art of medicine in our outpatient services which is probably a natural consequence of our relations with this type of patient Few doctors in private practice dare be completely truthful and outspoken in their relations with their patients There is no incentive in public clinics to have the patient come back for useless therapies or placebos since no fee is involved Owing to the number of patients the relatively brief period available for each one the physician's desire to see as many of them as possible and his primary interest in the abnormalities which they present or a feeling that they are only outpatients the human side of their problem has been neglected to a certain extent Sometimes we have been too ready to pass them *on to some other department*

Outpatients are just as human as private patients and although usually more easily controlled they require an equal consideration of their personal problems Often they go to the hospital because they want help, and only after considerable hesitation about doing so they are keenly appreciative of any manifestation of interest or sympathy The greater the intellectual gap between them and their physician the easier it is to establish an emotional relationship one of friendship loyalty

absorbent cotton DO NOT USE TOILET TISSUE Dry well with cotton and a powder or cornstarch or talcum

Cleansing with cotton and dusting with powder must be repeated with regularity about four times daily depending upon the amount of moisture and degree of itching The skin around the anus should always be kept clean and dry Cotton and talcum can be carried in separate envelopes on your person in a packet or handbag

Before retiring repeat the rectal washing and cleanse dry and powder the anal region After retiring rub a small amount of the ointment prescribed for you well into the skin about the anus This may cause burning for a few minutes Do not use mineral oil as a laxative, as it leaks from the anus to soil the surrounding skin

Do not become discouraged too soon

Report to on or about

Prescription for ointment mentioned

℞ Salicylic acid	1 0
Benzoic acid	2 0
Petrolatum q s	30 0

Medical Service

Name *Date*

INSTRUCTIONS FOR PATIENTS WITH ANEMIA

Patients with anemia easily become chilled and tired Therefore it is important for you to avoid cold and draughts Until you regain normal strength you should also take a rest during the day such as lying down for ½ hour after lunch and supper for weeks

If your stomach feels weak or if you lack a good appetite it is better to eat small amounts at each meal with an additional lunch between meals such as milk and Graham crackers or fruit The food should be simple Ideally meals should include 2 eggs or meat once daily (beef lamb veal poultry fish) green vegetables once daily (peas spinach carrots beets string beans) and fruit (prunes apricots apples peaches oranges etc)

If chewing is difficult because of absent or decaying teeth have them taken care of since you cannot properly chew your food with defective teeth and stomach trouble may result

It is advisable for you to have a blood count made once a year even if you feel well

Do not listen to friends who advise patent remedies (beef, iron and wine tonics) which are costly and useless Take the medicines prescribed by the doctor and no other medicine

Medicines advised 1
2
3

You may (may not) work

Report back on to

Medical Service

Name *Date*

CHRONIC BRONCHITIS AND BRONCHIECTASIS

1 It is important in this condition for patients to understand that the condition of their lungs is dependent upon infections of the nose sinuses tonsils and teeth
2 If you get a cold GO TO BED until you are entirely well In bronchiectasis colds often go down into the chest producing weeks of hard cough much sputum, and frequently pneumonia Do everything you can to avoid catching colds—avoid people with colds avoid crowded places avoid being chilled or exposed to very severe weather
3 Sleep in a room with fresh warm air Very cold or damp air will aggravate your cough especially if a cold is starting Air out the room before retiring then close windows for the night Sleep at least 8–9 hours a night
4 Dirty gums pyorrhea bad teeth are a constant menace—brush your teeth twice daily and have your teeth attended to by your dentist regularly
5 Eat a good diet—at least 2 glasses of milk meat fish or eggs fresh fruit or green vegetables daily
6 *Postural Drainage for Bronchiectasis*

Lie across the bed with your waist at the edge, leaning over with your hands on the floor or a low stool thus draining the lungs by gravity Place a large basin on the floor between your hands and gently cough out the material which should drain out Do this for from 1 to 10 minutes a time *for it* is necessary to keep the lungs free from secretion (2–3 times a day for most people)

and milk You must avoid fried and delicatessen foods Do not lose any weight unless your weight is above normal Avoid the use of iodized salt Do not indulge in alcoholic drinks Drink freely of water

4 Keep the bowels regular

5 *Remove blackheads before retiring at* night in the following manner Wash the face or affected parts with plenty of plain soap and hot water, or hot towel compresses soaked in boric acid solution before attempting their removal Steaming your face may also be of benefit *When there are groups of blackheads* centered in one place a small piece of adhesive plaster can be applied and left on overnight and removed the following morning

6 Apply the lotion prescribed with a piece of cotton or flannel wearing gloves to *prevent staining the nails* After washing or steaming at night, rub the lotion into all the affected parts with gentle massage, and apply a thin layer which is to be left on overnight In the morning repeat the same washing or steaming process and remove all lotions which are still adherent

7 Should irritation develop use the lotion every other night or every third night If the face becomes dry and rough under the treatment stop using the lotion temporarily and wash the face with soap and warm water or a starch paste diluted in a basin of warm water

8 If you have an important event to attend omit use of the lotion for two or three days before

9 All creamy preparations are harmful and are not to be used

10 Shampoo the scalp at least once weekly with plain soap and warm water

11 DO NOT PICK YOUR FACE IF YOU WISH TO AVOID SCARRING

12 DO NOT USE ANY MEDICATION INTERNALLY OR EXTERNALLY IN ANY FORM WITHOUT THE DOCTOR'S KNOWLEDGE

Medical Service

Name Date

INSTRUCTIONS TO THE PATIENT WITH ACUTE TONSILLITIS (SORE THROAT)

Sore throat is very contagious, and although you probably will not be able to give it to others when you go home, you should avoid kissing, sleep in a bed, and if possible in a room, by yourself, use separate dishes and towels for a few days Occasionally, from one to four weeks after a sore throat serious complications may occur so it is very important that you follow these instructions for the next 3 weeks and take good care of yourself

1 *Rest At least* 9 to 10 hours in bed every night Avoid getting tired

2 *Diet* Eat a good diet with plenty of fresh fruit and green vegetables

3 *Fluids* Drink at least 6 glasses of water a day between meals

4 *Colds* Avoid people with coughs and colds Do not go out unless absolutely necessary in stormy or cold weather and if so wrap up warmly

5 *If*—you have any pains in your joints, aching feet or muscles, if you have nose bleeds headaches puffiness of the face, or swelling of the ankles if you notice dark red or smoky urine or if you just feel tired and exhausted, *report to your doctor—this is very important—do not delay*

6 *Work* You may return to work after if you feel well

7 *Exercise* Regular exercise is good for you but use moderation for a week or so

8 *Medicines* Gargle your throat with hot *salt water three times* a day if it is at all sore An aspirin tablet dissolved in a glass of warm water makes an excellent gargle

9 YOUR TONSILS should (should not) be removed

Report to on M D

INSTRUCTIONS TO THE PATIENT WITH ANAL ITCHING (PRURITUS)

Whenever possible after defecation a rectal enema should be taken using a pint of plain tap water This should be immediately expelled A convenient method of taking the enema *is to use a rubber hand syringe* Cleanse the skin about the anus with wet

absorbent cotton DO NOT USE TOILET TISSUE Dry well with cotton and a powder or cornstarch or talcum

Cleansing with cotton and dusting with powder must be repeated with regularity about four times daily depending upon the amount of moisture and degree of itching The skin around the anus should always be kept clean and dry Cotton and talcum can be carried in separate envelopes on your person in a packet or handbag

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Medical Service

Name *Date*

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If chewing is difficult because of absent or decaying teeth have them taken care of since you cannot properly chew your food with defective teeth and stomach trouble may result

It is advisable for you to have a blood count made once a year even if you feel well

Do not listen to friends who advise patent remedies (beef iron and wine tonics) which are costly and useless Take the medicines prescribed by the doctor and no other medicine

Medicines advised 1
2
3

You may (may not) work

Report back on to

Medical Service

Name *Date*

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7 *Medicines*

1 Inhalation 1 teaspoon tincture of benzoin in a quart of boiling water Inhale the vapor 2 or 3 times a day for 15 minutes

2

3

4

8 *Smoking* This should be stopped—it is irritating and tends to produce cough

9 *Report to* *on*

M D

GENERAL INSTRUCTION FOR PATIENTS WITH BRONCHIAL ASTHMA

If you are sensitive to certain substances follow the directions given you for avoiding them You should (should not) keep a diet diary

1 All types of asthma are made worse by colds, sore throats, bad teeth, sinus trouble and diseased tonsils

a Avoid colds by keeping out of crowds avoiding overheating or chilling avoiding exposure to severe cold or storm, especially in the winter

b If you get a cold go to bed until you are well It will save time in the end

c Brush your teeth twice and day and have your teeth attended to by a dentist at least twice a year so that all bad teeth are removed or repaired

2 Avoid dusty, damp air and irritating fumes Air out the room thoroughly at night before retiring but only open the windows slightly during the night

3 Eat a good diet—adequate fruit and vegetables—and get at least eight hours sleep a night

4 Avoid worry and fatigue

5 Medicines

1

2

3

4

For an attack Attacks begin with severe coughing act immediately—do not wait for wheezing to begin

a *Adrenaline hydrochloride 1 1000*—hypodermically

Dose 3–10 minims (0 25 to 0 75 c c) give smallest effective dose and repeat in 20 minutes if necessary

b Adrenalin hydrochloride 1 100—use fine spray

Put nozzle at back of throat—squeeze bulb 2 or 3 times and draw a deep breath so as to get the vapor into the lungs Repeat every few minutes until you get relief

6 You (may) (may not) work

7 Report to on

M D

Medical Service

Name *Date*

CARDIAC DECOMPENSATION

1 *Rest* Stay in bed at least hours each night and lie down for one half hour after each meal

2 *Work* *No work*—except

3 *Exercise* Avoid any unnecessary exertion and any activity which brings on shortness of breath *Do not climb stairs* or hills except when absolutely necessary Walk slowly and rest frequently Avoid shopping trips

4 *Diet* Eat slowly do not eat heavily Eat a well balanced diet with fresh fruit, vegetables and meat at least once a day Do not salt your food at table

5 *Fluids* Do not drink more than glasses *total fluids* a day

6 *Weight* Watch your weight You should weigh about pounds If you begin to gain or are overweight consult your doctor It is vitally important to reduce

7 *Bowels* Do not strain Observe regular habits of going to the toilet Use *mineral oil if you need a laxative*

8 *Colds* Avoid catching cold Do not go out in very cold or stormy weather Avoid contact with people who have colds cough or the grippe If you do catch cold STAY IN BED UNTIL YOU ARE OVER IT

9 *If*—you notice increased shortness of breath swelling of the ankles cough or bloody sputum consult your doctor

10 *Women* Do not become pregnant

11 *Medicine* (1) Digitalis tablets (grains) a day at

You must always continue to take

your digitalis unless your doctor advises you to stop If you feel nauseated, vomit or have yellow vision, omit the tablet and consult your physician

(2)
(3)
(4)

12 Report to on

M D

Medical Service

Name *Date*

INSTRUCTIONS TO THE PATIENT WITH CATARRHAL JAUNDICE

You are recovering from an inflammation of the liver, and while you may expect to recover completely you must be careful for several months

1 *General* Lead a well ordered moderate life with at least 8 or 9 hours of sleep a night avoiding getting very tired

2 *Diet* Eat slowly It is most important to avoid all very rich greasy oily, fatty, or fried foods

Recommended	*A d*
Meat—le be f m tton b cken	Egg po k ham b f ed me t m ke el sardines
Fish—hal b t cod (ot f ed)	C am m etha 1 p tol b t t a meal
Ce e l and sk mmed m lk	Gra es d a sces
Bo l dor b k d pot t es m c ro e b d jell	Chocol t
Gre get bl	S lad d s gs d o ls
F sh f u ts a d f t)	

3 *Bowels* If you are constipated take 1–2 tablespoons of milk of magnesia

4 *Exercise* You (may) (may not) work

Other exercise

5 *Drugs* No medicines or drugs except those ordered by the doctor Cinchophen (atophan given for rheumatism) and vein injections of arsphenamine and other drugs used in the treatment for syphilis MUST NOT BE GIVEN

6 *Alcohol* This is to be strictly forbidden and avoided

7 *Medicines* 1
2
3

8 Report to on

M D

Medical Service

Name *Date*

CHRONIC LIVER CIRRHOSIS

1 *General* Live a moderate even life avoiding excess effort Go to bed every night at o clock If you are late in bed one night, make it up the next night One hour s rest in the middle of the day is recommended Take mild exercise (walking) out of doors every day Avoid becoming wet or chilled and if you have a cold or cough take extra care to get over it by going to bed

Visit the doctor regularly There may be changes in your diet or medicine which will become necessary as the time goes on

2 *Alcohol* Alcohol in any form is definitely and absolutely forbidden

3 *Diet* Relax and be seated when you eat your meals Chew your food carefully and eat leisurely Avoid large heavy meals Three small meals a day with a snack in the middle of the morning and one in the middle of the afternoon are recommended Daily, eat one or two eggs (not more) drink two glasses of milk Do not use the salt cellar Use only the amount of salt in your food which is employed in ordinary cooking Eat meat once a day and sparingly Eat no condiments One cup of coffee and one cup of tea are allowed daily

F d R omm nd d	*F d To Be Av ided*
I r be f lamb (st w d roasted ot fr ed)	P k l s usag w e s
T t k s	Pepper m tard lo e or th co dim t
C ndy Ic Cre m C e l	H y soggy p str es
R ce potatoe m caroni	F ed food
C t pe s t g b ns beets l ttuce	C bb g
Fresh or tewed f ts	B ked be s and b own b e d

Drink the equivalent of six glasses of water daily but no more In hot weather eight glasses are permissible

4 *Medicines*

Report to on

M D

Medical Service

Name *Date*

CHRONIC NEPHRITIS WITH EDEMA

1 *Rest* Stay in bed at least hours a night and lie down for hours each day

2 *Exercise No work*—except Exercise
3 *Diet* Eat slowly and do not over eat Have your *food cooked without salt* and do not add salt at the table Fish, eggs and meat can be eaten as follows

4 *Fluids* Drink glasses of fluid daily and no more
5 *Bowels* Should move regularly without straining use mineral oil if constipated
6 *Avoid* Chilling exposure, undue fatigue Avoid colds and above all sore throats If you catch cold go to bed and stay there until you are entirely well
7 *Brush Your Teeth and Gums* twice daily Have your teeth examined by a dentist once a year and repaired if necessary
8 *Alcohol* No alcoholic beverages
9 *Women* Do not become pregnant
10 *Warning* If you develop increasing swelling of the face or ankles headache nausea, vomiting or dark urine—see your doctor immediately
11 *Medicines* 1
2
3

Report to on

M D

COLLOID OR OATMEAL GRUEL BATH

Boil 2 cups of oatmeal in 2 quarts of water and strain the gruel through cheese cloth When cold add one cup of baking soda and dissolve Stir this mixture into a bathtub full of water as hot as you can stand comfortably Soak in a tub from 10 minute to 2 hours To prevent cooling the tub should be covered with a blanket On leaving the tub dry yourself by patting but NOT rubbing Leave some of the bath mixture on the skin This will stop the troublesome itching you have noticed but to prevent the skin from drying out use the fatty preparation the doctor prescribed for you

TREATMENT OF CONSTIPATION

Are You Really Constipated? Your bowels should move once daily but they will vary somewhat in frequency, amount and character, depending upon the nature of your diet and your habits of living If your bowels do *not move for two three or even four days* do not fret or worry over it, providing that this is not a common occurrence or if you are greatly underweight

Regularity Plan to have one regular time of day for going to stool and always go at that time, spend fifteen minutes if possible at stool and do not strain

Diet Avoid an incomplete or poorly balanced diet as this is a frequent cause of constipation Try to include in your diet daily
a Meat fish or poultry
b Milk—1 or 2 glasses
c At least one egg
d Two green vegetables selected from lettuce spinach, cabbage, string beans, peas, carrots broccoli etc
e Fruit at least twice daily
f Whole wheat bread To save expense, eat liberally of cabbage as a vegetable, and use canned tomato (2 cups) instead of fruit If you are overweight, eat sparingly of potato rice, macaroni bread, crackers cereals sweet desserts such as pie pudding cake and bananas

Salt Water Upon arising in the morning, drink two full glasses of water each containing one half tablespoonful of salt

Mineral Oil If you need further help, use mineral oil which is relatively non irritating two tablespoonfuls daily Keep up the salt water

Senna Tea If at all possible the use of cathartics should be avoided If however you must have more help senna tea may be used three evenings per week Six to ten senna pods are put into a glass of boiling water and allowed to stand until evening when the liquid is drunk Use the smallest number of pods possible to obtain the necessary result *Attempt to decrease the dose periodically*

Enemas Avoid enemas If you must use one use plain tap water or salt water (one teaspoonful to the quart)

General Advice As soon as possible one should try to discontinue all the foregoing instructions with the exceptions of the dietary advice and the formation of a habit time for going to stool

It is well to remember that there is no such thing as a need for the daily or 'weekly physic

Not all cases are alike and what has helped your neighbor may harm you Very hot or cold food should be avoided Ice water should not be consumed during meals Meals should be eaten at regular intervals

Medical Service

Name *Date*

CORONARY THROMBOSIS AND ANGINA PECTORIS

Because your disease is aggravated by stress and strain it is essential that you learn how to relax and take life easily and calmly Avoid worry excitement sudden exertion and fatigue as much as possible

1 *Rest* In bed at least hours every night and lie down hours daily
2 *Diet* Eat slowly do not eat heavily Lie down after each meal and relax Avoid very rich or heavy foods
3 *Weight* Keep your weight down to about pounds If you gain or are over weight consult your doctor and cut out starchy (bread potatoes cake spaghetti) and fatty foods (fried things etc)
4 *Bowels* Go to the toilet regularly at the same time every day Do not strain If you need help take mineral oil
5 *Fluids* Do not drink more than glasses in all of fluid daily
6 *Smoking* is prohibited
7 *Work* You are to do no work of any kind until
8 *Exercise* You should (should not) take some mild exercise each day Never exert yourself so that you become short of breath or have pain in your chest Walk slowly—avoid hills—avoid climbing stairs—avoid walking in the high wind Rest frequently
9 *Pain* If you have an attack of pain stop and rest IMMEDIATELY
10 *Drugs* You are to take the following medicines

If an attack lasts for more than a few minutes if you have severe indigestion or shortness of breath—call a doctor immediately

11 *Other Medicines*

12 Report to on

M D

Medical Service

Name *Date*

CONVALESCENT ACUTE NEPHRITIS

1 *Rest* Stay in bed at least hours at night and lie down for hours during the day
2 *Exercise* Avoid any unnecessary exertion
3 *Work* You should do no work until
4 *Diet* Eat slowly Do not eat any pepper, spices mustard smoked or pickled fish or meat Do not salt your food at the table Eat fresh fruit and vegetables daily Meat fish and eggs
5 *Fluids* At least glasses of fluid every day
6 *Alcohol* Do not drink any alcoholic beverages even wine or beer
7 *Weather* Do not go out of doors except in pleasant weather Avoid being chilled especially
8 *Colds* Keep away from anyone with a cold, sore throat or the grippe If you do catch cold go to bed immediately and stay there until you are entirely well
9 *Teeth* Brush your teeth and gums twice daily Have them examined by a competent dentist at least twice yearly
10 *Caution* If you develop
    a Pink or red urine
    b Swelling of the face or ankles
    c Headache
    d Nausea
    e Vomiting
    f Chills or fever
    CONSULT YOUR DOCTOR IMMEDIATELY
11 *Medicines* 1
    2
    3
12 Report to on

M D

INSTRUCTIONS TO DIABETICS

Name *Date*
Weight Pounds

You Have Diabetes Mellitus It is a disease which is characterized by the inability of the body to utilize or burn up sugars and starches as it should, with the result that sugar accumulates in the blood stream, the excess being passed in the urine This is due to the failure of the pancreas to secrete an adequate amount of the substance called INSULIN Improper use of sugar by the body leads to disorders in the utilization of other foods—proteins (meats and fish for example) and fats (butter and cream) The inability of the body to use these foods for the production of energy and in building body tissue is incompatible with life The immediate danger is DIABETIC ACIDOSIS—the symptoms of which are, weakness, drowsiness, severe thirst, difficulty in breathing nausea vomiting abdominal pain and finally unconsciousness If the diabetes is mild but uncontrolled there may be other disturbances over a long period of time—hardening of the arteries with subsequent heart trouble gangrene of the feet or legs, difficulties with vision, etc ALL OF THESE COMPLICATIONS ARE AVOIDABLE BY PROPERLY FOLLOWING YOUR SPECIAL DIET TESTING YOUR URINE AT REGULAR DAILY INTERVALS AND TAKING YOUR INSULIN DAILY AS REQUIRED AND IN THE PROPER DOSAGE

1 Diet

You have been placed upon a special diet It is highly important that you follow it strictly at all times and NEVER violate the amounts of food intake permitted in it TOO MUCH FOOD may lead to diabetic acidosis If you are taking insulin TOO LITTLE FOOD may result in insulin shock (Symptoms are hunger, weakness faintness, paleness crying, nervousness sweating abnormal laughing fright, excitement mental confusion double vision and unconsciousness Therefore always eat ALL of your diet because it has been calculated for you upon the basis of your body weight and the amount of physical activity you undergo daily If you are taking insulin your insulin dose has been measured for the the amount of food in your diet As an added safety, always carry a lump of sugar in your pocket or purse and eat it immediately if you feel any of the symptoms of an insulin reaction It is also important for you to eat your meals at regular hours so that you will not be without food for a long period of time A diabetic should not be fat and should always be a little hungry

2 Urine

Test your urine regularly and keep the results of each test in a small book to show your doctor each time you see him From these results he can tell you how well your diabetes is being controlled If your urine shows continuously red tests at any time (Benedict's Solution as the test material), SEE YOUR DOCTOR IMMEDIATELY

Eight drops of urine—not more or less—are placed in a test tube and to this is added a teaspoonful of Benedict's Solution Shake tube gently to mix, place tube in upright position in a pan of boiling water, and keep for 5 minutes with the water still boiling The tube is then removed and the color determined. Shake before reading the color

Blue	No sugar in the urine
Heavy Green Precipitate	Trace of sugar
Yellow Sediment	Moderate amount
Red Sediment	A large amount—see your doctor if this continues

Record these as colors in your notebook

If you are using the GALATEST powder for testing your urine for sugar, you have but to follow the simple directions which come with each tube of powder and match the color obtained with the color chart for the percentage of sugar present in your sample of urine Record these as percentages in your notebook

Test urine at times specified below

3 Insulin

You (DO) (DO NOT) have to take insulin On the basis of your diet severity of your diabetes weight and the amount of physical activity you have been placed upon a special dose of insulin Boil the needle and the two parts of the syringe for five minutes each time

before using Remove wire from the needle NEVER TOUCH END OF THE NEEDLE WITH THE HANDS Attach the needle to the syringe and put the syringe together Tweezers are good for this purpose and can be purchased at the *Ten Cent Store* and either boiled each time or kept clean in a small bottle of 95% alcohol Next wet a small gauze of cotton with alcohol and cleanse the top of the insulin bottle Using care not to touch the needle push it through the rubber stopper having the plunger pulled back to the point of dosage first Next invert the insulin bottle and push air into it and withdraw the amount of insulin as directed Still being careful not to touch the needle to anything lay it down and with one hand pinch up a fair amount of skin and flesh and rub briskly with an alcohol sponge Next insert needle as you have been directed and press plunger till all of the insulin is out Quickly remove the needle and rub the area for about 3 minutes

YOU ARE TO TAKE INSULIN AS FOLLOWS

unit of insulin every morning ½ hour before breakfast Each cubic centimeter of this insulin contains units so that c c is the amount of insulin you require In addition you are to take daily units of insulin or c c at A M P M When you buy insulin get U 40

4 General measures

Care of Feet Bathe feet daily in warm soap and water and rub with rubbing alcohol Always dry thoroughly between the toes Dry by pressure rather than by vigorous rubbing When thoroughly dry apply lanolin ointment to keep the skin soft Watch the feet carefully for any broken skin or sore and report it to your doctor Wear soft comfortable shoes New shoes should be worn for only 15 minutes each night before going to bed until they are well broken in Have your doctor or nurse examine your feet regularly

Care of Nails Trim nails with scissors only and use nothing but sandpaper for callu es Take care not to break the skin Cut nails straight across Do not apply bandages to toes or feet unless instructed to do so by your doctor

Weight Watch your weight carefully If you are fat you should lose weight on your diet If you are gaining weight and are already fat your diet is not right or you are NOT following it

Other *Never drive a car unless you have* taken some carbohydrate food within two hours Should you develop a slight cold or slight indisposition and do not feel like eating DO NOT STOP YOUR INSULIN BECAUSE YOU NEED IT NOW MORE THAN EVER

Carry a card on your person always stating that you are a diabetic and are or are not taking insulin

Living alone can be considered a hazard for a diabetic

See your doctor at regular intervals
Report to on at
A M P M

Unless you carry out these instructions, the time spent in the hospital has been wasted

INSTRUCTIONS TO THE PATIENT TROUBLED WITH FLATULENCE AND BORBORYGMUS

Noises produced by gas in the intestinal canal and by its expulsion from the rectum are very annoying and embarrassing but this condition can be alleviated by your adherence to the following foods Generally speaking roughages starches leguminous plants and onions should be eliminated from the diet entirely

Foods Not Likely to Cause Gas

Vegetables especially green artichokes asparagus spinach string beans green peas cooked celery summer squash and French carrots

Limited quantity of boiled baked or mashed potatoes

Rice barley farina cornstarch arrowroot oatmeal cream of wheat and other ordinary cooked breakfast foods

Water tea milk and buttermilk

Fresh meat or fish (white) or game or poultry once a day

Eggs in moderation Cottage cheese Limited amount of butter

Toast bread or zwieback Plain cake and puddings

Fresh fruit apples grapes pears figs peaches oranges grapefruit pineapple juice

INSTRUCTIONS TO DIABETICS

Name *Date*
Weight Pounds

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2 Urine

Test your urine regularly and keep the results of each test in a small book to show your doctor each time you see him From these results, he can tell you how well your diabetes is being controlled If your urine shows continuously red tests at any time (Benedict's Solution as the test material), SEE YOUR DOCTOR IMMEDIATELY

Eight drops of urine—not more or less—are placed in a test tube and to this is added a teaspoonful of Benedict s Solution Shake tube gently to mix place tube in upright position in a pan of boiling water, and keep for 5 minutes with the water still boiling The tube is then removed and the color determined Shake before reading the color

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If you are using the GALATEST powder for testing your urine for sugar, you have but to follow the simple directions which come with each tube of powder and match the color obtained with the color chart for the percentage of sugar present in your sample of urine Record these as percentages in your notebook

Test urine at times specified below

3 Insulin

You (DO) (DO NOT) have to take insulin On the basis of your diet severity of your diabetes weight and the amount of physical activity you have been placed upon a special dose of insulin Boil the needle and the two parts of the syringe for five minutes each time

5 *Weight* It is vitally important for you to keep your weight down You are (are not) overweight You should weigh about pounds Weigh yourself every few weeks and if you gain or are are overweight cut down on bread, potatoes candy sweets cake, butter, cream etc and eat less

6 *Fluids* Drink at least 8 glasses of water daily

7 *Bowels* See that your bowels move regularly Do not strain If constipated take 1–2 tablespoons of mineral oil at night and drink several glasses of water on arising in the morning

8 *Colds* Try to avoid catching colds by avoiding people with colds and keeping warm If you get a cold go to bed until you are well

9 *Teeth* Brush your teeth and gums twice a day Have your teeth examined by a dentist once a year and repaired if necessary

10 *Women* Do not become pregnant

11 *Medicines* 1
2
3

Report to on

M D

MANAGEMENT OF OBESITY

Name *Weight*
Date

It is only with your full cooperation that favorable results can be obtained Your desire to reduce your weight is justifiable not only for social reasons but because being over weight is injurious to your health and long life

Throughout your reducing regimen your *general health must be carefully and competently safeguarded* It is much safer to reduce slowly than to lose weight rapidly You must not depend upon drugs alone to do the work When taken without proper supervision drugs will injure your general health

Be careful not to accept anyone s recommendations about patent drugs The majority of cases of obesity are due to overeating and lack of exercise To reduce safely and effectively you should follow a properly balanced *diet and take the required amount of such* exercise as golf tennis riding swimming walking etc

Diet Follow this diet strictly (1500 calories—carbohydrates 155 gm , protein 70 gm , fat 65 gm)

B kfa t

lued ng
C real ½ cup
Egg—1
Sl e toast—1
Butter 3 t aspoo s
M lk—1 gla s

D ne

Le n meat o fish 1 p ece 3 x 3 x ½ thick
Cottag h ese—2½ *rounded tablespoons*
Veg t ble—½ cup (tomatoes caul flow cabb g t ng be ns b oc l squash)
V getabl —½ cup (b ussel sprouts turn p pumpk beets carrots onio s green pe)
Fru t—1 c p
B ad—1 sl ce
Butter—2 t aspoons
M lk—1 glass

Supp

Meat or fi h—1 p ece
Potat e—½ cup
Veg table—½ cup (t m toes w t cress l flow r egg plant bbag green peppe s umm r qua h young str g beans leek)
V g table—½ cup (st ng beans pumpk n turn p squ h be ts ts on o s y g green pea kr bru l p o ts)
Fru t—½ cup
B d—1 sl
Butt —2 teaspoo s

You are overweight and should weigh about lb Anything more than this is a strain on your heart It is possible for anyone to reduce by eating less than he needs so that the body uses its own fat for food and weight comes off

On one day each week eat nothing but two bananas and four glasses of skimmed milk Weigh yourself every week on the same day same time and same scales You should lose 2 lbs a week

If you do not lose weight on this regime cut out more of the fatty and starchy foods you are eating too much If you lose more than 3 lbs a week you may eat a little more

Exercise

Use saccharin for sugar and mineral oil for salads Eat no ice cream candy or pastry Eat no greasy or fried foods Do not drink over 6 glasses of fluids daily Milk water tea and coffee are included in this list

Report to on

Medical Service

Name *Date*

Salads of lettuce and other fresh green vegetables, raw or cooked

Foods to Avoid

Meats Canned, spiced, preserved and salted
Fish Herring, sardines in oil, mackerel salmon, shellfish
Stews—goose, domestic duck, oysters
Old cheese, cream cheese, except cottage cheese
Dry beans, corn, sprouts cole slaw cabbage, cauliflower sauerkraut, raw vegetables, garlic and onions
Rich soups, berries, figs preserves, gravies, nuts sweets, pie, pastry fats, oils and alcoholics

Other

Reduce your fluid intake to 2 quarts daily Dry heat or hot compresses applied to the abdomen will afford comfort A soapsuds enema will often relieve an attack Mild laxatives such as petrolagar frequently control the tendency to excessive gas formation

FLAXSEED POULTICE—INSTRUCTIONS FOR PREPARATION

To about 300 c c of water (boiling) add slowly and with constant stirring enough ground flaxseed to form a thick paste Usually about one cupful of flaxseed will be required Add ½ teaspoonful of baking soda and beat well Spread on cloth cover with flannel and place on anointed skin

CAUTION Do not leave poultice on the skin long enough to burn the patient

INSTRUCTION TO THE PATIENT WITH CHRONIC GALL BLADDER DISEASE

You have a chronically diseased gall bladder It has been decided that this will not be removed surgically at present Proper diet and care will enable you to be much more comfortable

1 You should always stop eating before you feel "full"
2 You should eat
   Lean meat (beef fowl lamb) Any vegetables or fruit Bread potatoes rice and macaroni Eat enough to keep your weight about lb Simple desserts such as puddings, jellies and custards
   glasses of water a day including one glass of hot water before breakfast Coffee with sugar and milk in the morning only Tea with sugar Clear soup if desired
3 You *should not* eat
   Any fried foods Veal, ham bacon, pork game, mackerel, bluefish, eggs heavy sweets, pastry, heavy cream, chocolate, cocoa olive oil, gravies
4 Call your doctor if
   You have severe pain in the abdomen lasting more than one hour
   You vomit more than once
   Your eyes or skin turn yellow
   Your urine is dark or your stools are light or clay colored
5 *You will probably have a moderate* amount of indigestion gas, or distress at times which cannot be entirely relieved Gas may be relieved by sipping very hot water
6 Your bowels should be kept regular by taking
7 Other medicines 1
   2
   3
8 You (may) (may not) go back to work
9 Report to on

M D

Medical Service

Name *Date*

HYPERTENSION AND CHRONIC NEPHRITIS WITHOUT EDEMA

1 *Rest* In bed at least hours a night and lie down hours every day
2 *Exercise* You should get some regular exercise, such as walking each day, but you must avoid sudden strenuous exertion or getting very tired or short of breath
3 *Work* You may (may not) work
4 *Diet* Eat slowly do not overload your stomach Fresh fruit and vegetables every day if possible You may eat fish meat or eggs

PERNICIOUS ANEMIA PATIENTS

You have pernicious anemia A few years ago this was almost always fatal hence the name 'pernicious' but today you can expect to improve and remain well ON ONE CONDITION—*that you continue to take liver* Once a person feels well there is a great temptation to stop treatment, and that is your greatest danger, because, if you do stop, the disease will steal back on you so insidiously that before you realize it, or take the trouble to call a doctor it may be TOO LATE to prevent permanent damage to your nervous system or possibly even to save your life *You must continue to take liver all your life*

1 *Liver* We recommend that you
   a Eat (raw cooked) liver lbs times a week
   b Take 's Liver Extract
   c Report every for an injection of liver extract at
2 *Diet* Eat a well rounded diet with meat fish or egg green vegetables and fresh fruit at least once a day
3 *Exercise* You (may) (may not) work
4 *Rest* Get at least 8 hours of sleep a night Avoid undue fatigue
5 *If* You notice that there is tingling or numbness of your hands or feet difficulty in walking or controlling your urine, or that you do not feel well in any way—do not delay—but consult your doctor at once
6 *Medicines* 1
   2
   3
   4

Report to on

M D

Medical Service

Name *Date*

PNEUMONIA

You have just recovered from pneumonia but you should realize that following a severe fever like pneumonia it will be some weeks until you are entirely well and you should follow these instructions

Spend at least hours in bed daily for weeks

Sleep in a warm room, open the windows only slightly

Go outdoors only on fine days when you feel up to it and wrap warmly

Eat a well rounded diet You should gain weight

You may return to work in weeks if you feel well and no complications ensue

Remember that if you have had pneumonia once it means that you are more apt to have it than the average person Most people get it when they do not take care of colds and coughs when they undergo severe exposure or are very tired or run down Therefore

1 Avoid people with colds
2 Avoid exposure to severe cold or storms when possible
3 Do not let yourself get tired and run down eat a good diet and get at least eight hours sleep daily
4 If you get a cold or persistent cough, stay in bed until you are well It will save time in the end
5 If you are a drinker, cut out the alcohol Whisky does not ward off pneumonia

You were given (serum—type) (sulfathiazole) (sulfadiazine) (sulfamerazine) (penicillin) in the treatment of your pneumonia Some doctor at a future date may want to know this fact

Medicines 1
   2
   3
   4

Please report to on

M D

Medical Service

Name *Date*

RECURRENT PYELITIS AND PYELONEPHRITIS

If you have once had pyelitis you are very apt to have it again As each attack is likely to damage the kidneys it is very important to try to avoid further attacks The best way to do this is to lead as healthy a life as possible Get plenty of sleep good food and exercise avoid cold fatigue and exposure

1 *Rest* In bed at least hours a night Lie down hours a day
2 *Diet* Try to get meat fish or eggs a green vegetable fresh fruit and 1-2

PEPTIC ULCER

You are suffering from an ulcer of the which (showed) (did not show) in your X ray study An ulcer heals slowly, and unless you take good care of yourself for months and perhaps years, you may have very serious trouble On the other hand, if you will take care of yourself you neet not worry about it, and should be able to lead a fairly normal life

Nervous tension, worry and fatigue make ulcers worse If your work keeps you tense or you feel upset a lot of the time, you must learn to relax and work more calmly Stop a few minutes every now and then throughout the day and relax If you feel tired and run down you should and must get more sleep and rest The worst effects of nervous tension are at meal times, because it affects the nerves of the stomach and leads to pain and indigestion Therefore, never eat a meal hurriedly It is well *not to eat alone If you feel nervous or* hurried before a meal lie down and relax a few minutes before eating Then eat slowly, and afterwards sit down quietly for a few minutes

If you had an open sore on your hand you would not rub sand into it, nor would you irritate it You would try to keep it covered and would protect it Similarly an ulcer, which is an open sore on the lining of your stomach, must be protected *First*—chew your food *thoroughly, so that it is well softened* when it enters the stomach If your teeth are poor or missing have them attended to or replaced *Second*—avoid rough, irritating foods in your diet, vegetables should be strained or pureed to remove the rough portions *Third*—avoid acids alone because they irritate the ulcer and lead to pain Fresh fruit, fruit juices and tomatoes are acid foods and should be taken *only* with other foods The stomach itself secretes acid especially when meat and fish is eaten Therefore meat should not be eaten in large amounts or by itself The stomach s own acid is very irritating when the stomach is empty so you should always eat something between meals Milk is best because it is soothing and neutralizes acid but chocolate milk shakes cocoa and egg nogs will do as well All those points are taken care or by the Convalescent Sippy Diet which you have been given but you should know why you are to follow these rules

As time goes on your ulcer will heal, but do not give up the diet, except on your doctor's advice You do not need to be an invalid many doctors with ulcers have worked for years taking care of themselves all the time, and if you will follow the few important principles of diet, relaxation and avoidance of fatigue you will be able to live perfectly normally There are certain times of the year when your ulcer will be likely to trouble you—usually it is the same time each year or twice yearly for each individual Accordingly—be on your guard at these times of the year when you have had symptoms in the past If you feel any pain or have indigestion, gas, black or dark green stools, see your doctor, go to bed for a few days and go back to the diet of frequent small feedings of milk and eggs As your symptoms disappear, gradually increase your diet again If you would heed these first warnings of slight *pain or indigestion you might* avoid a long period in the hospital

To Sum Up Then

1 Avoid fatigue—get at least 10 hours of sleep a night
2 Try to avoid nervous strain and worry No arguments or controversies!
3 Relax at meal hours—regular meal hours eat slowly chew your food well sit or lie down for a few minutes before or *after meals*
4 Avoid rough irritating foods (bran, raw fruits or vegetables)
5 No alcohol—not even beer and wine
6 No tobacco—if a cigarette helps you relax after meals that is all right, but no more
7 Keep something in your stomach—by taking milk etc every 2 hours and at night before bedtime
8 Heed very slight symptoms—rest and restrict your diet to frequent small feedings of milk, cream and eggs and avoid weeks in the hospital
9 No work until
10 Medicines 1
2
3

Report to on

Medical Service

Name *Date*

5 On the fourth night remove the ointment Scrub yourself with soap and hot water Change all underwear sheets, pillow cases etc
6 If any other members of your family suffer from scabies they *MUST* be treated otherwise your cure will be hindered by re infection

Report to on

M D

HOW TO ADMINISTER A SEDATIVE BATH

Immerse the patient in a tub except for his head at a temperature of 100–102 F (not above) Allow him to remain in the bath from 10 to 30 minutes depending upon his reaction Keep cold applications on his head Upon removal from the tub wrap quickly in warm blankets Take particular care to keep the feet warm

INSTRUCTIONS TO SINUS SUFFERERS

You are suffering from a disease which can be cured Most patients get permanent relief the exceptions being a few chronic neglected cases A climate with violent changes of temperature is not ideal for you The responsibility for a cure either temporary or permanent must not be placed upon the doctor Your cooperation is most essential The following instructions faithfully carried out will help to bring about satisfactory results and prevent recurrences Treatment should not be discontinued until a cure has been effected

Wet Hair Be careful not to leave the house or ship with wet hair in either cool or cold weather

Chilling Sudden chilling of the body such as results from leaving a hot room, galley engine room and going into the cold out doors or taking cold drinks after becoming heated by dancing or other exercise should be avoided Avoid drafts

Work Overwork and exhaustion will break down your resistance and bring about a relapse of your trouble even when you are apparently cured Do everything in moderation

Wet Feet Avoid chilling your feet or wetting them Do not step out of bed on to a cold deck or floor Keep your slippers always handy Wear rubbers and a raincoat on rainy days

Swimming and Diving Although diving is absolutely contraindicated we do not object to swimming and bathing, provided it is done judiciously To sit on the beach on a cool day in a wet bathing suit is a bad practice generally and especially harmful to those suffering from sinus trouble Do not stay in the water until your lips are blue and you are chilled

Clothing Do not go out in cold weather without a hat Do not wear summer shorts in the Winter time Wool or woolen mixture should be worn in cooler seasons

Food and Elimination Eat healthful and easily digestible foods rich in vitamins such as fruits vegetables milks and eggs Overloading the stomach is not good for you See to it that your bowels move regularly

General Hygiene Avoid worry Keep your skin teeth and stomach in good condition as they are part of the general mechanism Lowered general health can and does produce sinus disease in a susceptible person

Smoking and Drinking Alcoholic beverages should never be indulged in other than moderately It is better to avoid both entirely

Nasal Irrigations Do not irrigate your nose, lest you infect your ears DON T BLOW YOUR NOSE HARD

If you have a temperature you should rest in bed in a warm room The room should not be cooled off at night The humidity of the room is kept between 35 and 45 per cent and this can be accomplished by having steam from a teapot going in the room for 10 minutes or so each hour You should inhale steam for from 5 to 10 minutes every two hours if awake This can be done by taking a thermos bottle of boiling water to bed with you or by placing a quart of boiling water in a thick pitcher with the top of the pitcher closed by a paper bag A small hole is torn in the bag at one bottom corner You can inhale the steam through your mouth and exhale it through your nose If the bed clothes become wet often change to dry clothes Drink at least 3000 c c of fluids daily

Pain Empirin compound tablets one or two every three hours during the day Don't

glasses of milk a day Cooked cereal and whole wheat bread are also good

3 *Fluids* Drink at least glasses of fluid a day

4 *Bowels* A good diet and a regular habit of going to the toilet at the same time each day will take care of them Use mineral oil if constipated

5 *Alcohol* Do not drink alcoholic beverages

6 *Work* You (may) (may not) work

7 *Exercise* Moderate exercise every day will help you to keep fit Do not do anything that exhausts you or makes you short of breath

8 *Colds* Avoid people with colds sore throats or grippe, avoid crowded places in Winter avoid getting chilled or over heated If you do get a cold, go to bed until you are well

9 *Teeth* Brush the teeth twice a day and have your teeth attended to twice yearly by your dentist

10 *Attacks* If you have a pain in the back burning urination chills, fever or head ache go to bed drink a glass of water every hour call your doctor and stay in bed until you are well

For the headache—2 aspirin tablets every 2 hours till relieved

For the pain—Hot water bottle to the back—wrap in a towel

For burning—Take a teaspoon of baking soda in water every 3 hours

If you feel tired all the time if you have dull headaches nausea vomiting shortness of breath or swelling of ankles consult your doctor

11 *Women* Do not become pregnant until you have asked your doctor s advice

12 *Medicine* 1
2
3

13 Report to on

M D

Medical Service

Name *Date*

RHEUMATIC FEVER INSTRUCTIONS

If you have once had rheumatic fever you are more likely to have it again Since each attack is likely to damage the heart you must do everything possible to avoid further attacks Most attacks follow colds and sore throats therefore try to avoid colds as follows

1 Keep away from people who have colds
2 Keep away from crowds, theaters, especially in the Winter and Spring
3 Avoid getting overheated or chilled, avoid exposure to severe cold or storms

If you should catch cold, go to bed until you are *entirely* well Every cold or sore throat is a serious threat to your health

Teeth Brush your teeth and gums twice a day Have your teeth examined by a dentist at least once a year, and repaired if necessary

Sleep Sleep in a bed by yourself and if possible in a room alone At least hours in bed every night and lie down hours a day

Diet Meat or eggs once a day, 2 to 3 glasses of milk a day, an orange a grapefruit lettuce or tomatoes every day if possible

Exercise No work until

Other exercise

Medicines 1
2
3

It is advised that your return to have your tonsils removed

Be sure to follow these directions It may save your a great deal of time and trouble later on and will surely prolong your life You have a disease which tends to recur and you must learn to live a healthy life and avoid these recurrences which put a heavy strain upon your heart

Report to on

M D

MANAGEMENT OF SCABIES

1 Dust all bed sheets and bed spreads with sulfur powder
2 Scrub thoroughly the first night from the neck down with soap and hot water
3 Rub each individual pimple with the ointment prescribed and spread from there onto the normal skin without using any more ointment and avoiding the face and neck
4 Repeat treatment in the morning and evening for three days but do not bathe

Eggs	Sponge cake
Meats	Angel food cake
Fowl	Custards
Fish	Puddings (rice
Soups	cornstarch
Milk	tapioca)
Buttermilk	Gelatins
Cheese	Potatoes
"White cereals"	Bananas
(rice farina,	Avocado pear
cream of wheat)	Fruit juices
White breads	Tea
White crackers	Coffee
Macaroni or	Cocoa
Spaghetti	

Avoid Raw or cooked vegetables no raw or cooked fruits because of their cellulose content honey molasses, maple syrup fudge sauce heavy frosting on cakes and candies are avoided because they are fermentation formers

It makes but little difference whether the foods allowed are fried broiled or baked

6 You should have some bulk producing substances in your diet such as agar agar in finely powdered form or in cereal form—or you may choose some of the following derivatives of psyllium seed such as Metamucil—Konsyl—or Mucilose The average dose of these preparations is two to three heaping teaspoonfuls daily taken preferably in two or three doses spaced through the day If cold water is used and the mixtures are not allowed to stand for any period of time but rarely will there be any unpleasant taste noticed

7 Notify your doctor if any of the following symptoms arise or are especially troublesome 1) increasing loose watery stools 2) abdominal pain 3) nervousness or spasm

8 *Returning to Your Regular Diet* First the coarse breads and cereals later the milder cooked vegetables and fruits later raw vegetables and fruits are used to build up the diet If any discomfort results from returning to vegetables step back to the blander diet level for a few weeks and then try the addition again If the stools are loose and frequent reduce the amount of bulk producer or the amount of roughage in the diet

SOME THINGS YOU SHOULD KNOW ABOUT *SYPHILIS*

Syphilis is a very common disease At least four or five million people in this country have syphilis Every year more than a million persons in this country become infected with this disease Almost half of those who have it are women and children Most of these have contracted the disease before they were thirty years old More than half of the infected either do not know they have syphilis until many years after infection, or do not take enough treatment to cure it when it can be cured

Too many patients with syphilis stop treatment when the sore rash or other symptoms have gone or as soon as the blood tests become negative They think the disease is cured because they do not know syphilis or how it behaves Years later they go back to their doctors with new and more serious troubles only to learn that they still have syphilis and that the disease is in the late stage which is hard to cure and which cripples and kills

If you know what syphilis is you will also know very well that you must make up your mind to conquer the disease just as you make up your mind to meet any of life s problems If you decide to keep syphilis from destroying you you will also decide to do the following things

You will see a doctor who knows how to treat syphilis and then take his advice about how much treatment is needed

You will stick to treatment even though it takes so long that it is easy to become discouraged

You will stick to treatment even though it is hard to get to the doctor s office the weather is bad and much time is lost in travel and waiting

You will take enough treatment to prevent trouble later on, as well as to get rid of the sore or rash or other symptoms which worry you now

You will stick to treatment even when it hurts and sometimes makes you sick

You will do everything you can to keep from giving anyone else syphilis

If you are a good patient and a good citizen you will do all you can to help your self and protect others Only feeble minded

take these at night as they contain caffeine and may keep you awake

You (have) (have not) nasal polyps and (need) (do not need) an operation

Report to on

M D

THE SPASTIC AND IRRITABLE BOWEL—MANAGEMENT

You have a condition called "spastic colon" or irritable bowel It is a condition of adult life rather than of childhood, and affects both sexes about equally It occurs especially frequently in individuals living under stress and strain and tension Teachers professional workers, executive heads in business are common suffers—as are also individuals bearing too great a burden such as children supporting ill parents, wives supporting stricken husbands, or widows raising children under financial difficulties Another large group of patients have slipped into this condition by following food fad which have led to unbalanced diets or by the use and abuse of cathartics when trying to rid themselves of the so called auto-intoxication"

Irregular habits are important causes and this is especially true of irregular bowel habits Irregularity of evacuation or ignoring the urge for defecation will tend to lessen the normal reflex and increase constipation Irregular eating habits and the habit of eating rapidly tend to distort the normal rhythmic activities of the bowel The repeated stimulation of the bowel reflex by the repeated ingestion of very hot or very cold drinks may lead to a disturbance of intestinal motility, particularly increased motility resulting in a loose stool The use of roughage and health foods likewise causes increased stimulation of the intestine and this may well lead to diarrhea or constipation Eating meals hurriedly only serves to increase the nervous tension because the food is not well chewed so that an overburdened nervous intestinal tract has an added load to carry If people who complain of bowel trouble and who believe that they must take something to promote regularity would only allow themselves sufficient relaxation and adequate time to be regular about going to the toilet sleeping eating and playing a good portion of their trouble would cease

The use of laxatives cannot be too strongly condemned Too often, because of erroneous ideas about the physiology of the bowel the patient embarks upon a 'Cathartic career" He fears so called auto intoxication or he believes he should have more frequent and more copious stools and therefore uses a cathartic

Since the trouble is in the last few inches of the digestive tract, why not attack the trouble at its source by using a small enema or suppository? Why clean out twenty odd feet of intestine to remove a plug at the lower end? Unfortunately many patients do not stop at this point for having produced a 'better bowel movement' they cannot understand why they cannot have a movement the next day Believing themselves again constipated and not realizing that the cathartic over-emptied their bowel, they take another laxative and so the vicious cycle continues

The bowel-conscious American public is the product of not only the friendly neighbor s advice to use liver pills or blatant press and radio advertisements but also sometimes inadvertently the medical profession There is a subconscious desire for the human being to empty his gastro intestinal tract when there is some bodily discomfort Because of this deeply rooted instinct the patient believes that any time he feels any discomfort, a laxative should be part of the treatment

1 The value of rest—physical and mental is inestimable Longer hours of sleep and if possible a mid day or mid afternoon rest is important

2 You should learn to live within your energy capacity and when the outgo or demand is taking more from you than you can normally replace you must take time off to rebuilt your energy supply just as a weak automobile battery is recharged before it is completely exhausted

3 If you are using ANY cathartics mineral oils, etc discontinue them immediately

4 Drink one or two glasses of hot water before breakfast and go to stool regularly after breakfast

5 *Diet* The diet should be smooth or bland that is non irritating and smooth and soothing Start with foods elected from the following

the same way You will be given injections in the arm either with or followed by eight to twelve injections of bismuth, given in the hips

Any itching rash vomiting diarrhea, sore mouth bladder trouble must be reported to the doctor at once Sometimes for one reason or another you cannot be treated in the usual way Have confidence in your doctor and depend upon him to know what is best for you in the way of treatment

It Is Up To You

If you think you know who gave you syphilis tell that person to be examined It would be most selfish and unfair not to give that person the same chance to be cured that you are having If you cannot or do not want to tell that person yourself ask your doctor to see to it He will be glad to co operate If there is the least danger that you have given syphilis to your wife husband children or to any other person they should be examined They have just as much right to treatment as you have A woman with syphilis will have babies with syphilis, or they may be born dead

If you are single do not marry until your doctor says it is safe, or you may give your wife or husband the disease

If you have active syphilis—you must follow these rules until the doctor says it is no longer necessary

1 No sexual intercourse or a petting party Sleep alone

2 Do not kiss anyone Sores in the mouth are very dangerous

3 Do not let anyone use your drinking cup dishes tooth brush tooth paste towel *razor handkerchief pipe lipstick or any* thing which may have touched sores in your mouth or on your body

4 Never use a public drinking cup or fountain

5 Never let a barber shave you

6 Never go to a dentist unless you tell him that you have syphilis

7 Stop work until any exposed sores or rash or sores in the mouth are healed, if you do any work that brings you in close touch with other people

8 Stick to treatment—intermittent treatment will NEVER cure syphilis

9 Brush your teeth twice daily Don t use a brush with stiff bristles

10 The fact that you are traveling is little excuse for your not receiving treatment There are Out patient Offices and Public Health facilities in all large cities where you can receive treatment FREE—and in many cases—any hour of the day or night

11 It is not a good idea to go from doctor to doctor However should this be necessary there is no reason why your treatment should suffer if you at all times keep your treatment card where you can get it Have the first doctor treating you make out a full treatment card for you so that wherever you may be your treatment will be carried out as it would have been done had you been able to stay under the care of your first doctor

12 After you are discharged at the end of your treatment, and have had a thorough physical examination have a blood test made once every six months if possible and at least once a year

13 Any doctor consulted later for no matter what disease should always be informed of the previous existence of syphilis The life of the patient might well be the price he would have to pay for negligence in this regard

14 Pay no attention to certain claims made in papers or magazine articles about certain new methods of treatment in the research stage as of this writing Your doctor is acquainted with these methods and when and if you are considered a favorable risk for such treatment, you will be so advised how and where to obtain such treatment

This paper has been written for you It is hoped that you will benefit by the information set forth

FREQUENTLY USED PRESCRIPTIONS

The following frequently used prescriptions are included for the convenience of the House Officer as are dosages of commonly used drugs

Tr Hyoscyamus Mixture

Tr Hyoscyami	30 c c
Potass Citrate	30 gm
Water to	120 c c

Sig 1 teaspoon t i d p c

and childish people and those who do not know what syphilis is, need to be reported for non cooperation in treatment

Syphilis Is a Dangerous Communicable Disease

Syphilis has been called many names, such as pox, blood disease hard chancre 'old Joe' and lues, but syphilis is the right name Syphilis and gonorrhea (clap) are entirely different diseases, caused by different germs One never results from the other, but a person may have both diseases at the same time

The Stages of Syphilis—Their Symptoms and Signs

If a person has sexual intercourse with, or kisses another person who has the sores of syphilis on the private parts or in the mouth, *or touches the sores in any way the germs may* pass from the one who has the disease to the other They then penetrate through the skin or the lining membranes of the private parts or the mouth and begin to multiply In less than a day, many of them are carried by the blood stream to all parts of the body From three to six weeks later, there may be a lump or sore where the germs first went in and the glands near it may begin to swell The sore near it may look like a small pimple or a 'cold sore' or, it may be a big ulcer It is called a hard chancre It is full of germs and very dangerous to anyone who touches it Many infected people especially women, never see the chancre because it is hidden in the water passage or in the private parts *or in the mouth* and it usually does not hurt Many others think it is nothing serious and do nothing about it

The sore will heal sooner or later, EVEN WITHOUT TREATMENT, and the patient may think that the disease is cured or that the pills his friend told him to take cured him A few weeks later some of the many signs of the secondary stage of syphilis may appear, such as a rash on the skin small painless sores in the mouth or on the private parts Headache fever, sore throat, swelling of the glands all over the body, pain in the bones brown spots on the palms and soles and falling out of the eyebrows and hair There may only be a few of these signs and they may be so mild that scant attention is *paid to them In some cases* if the disease is not treated as it should be these signs may come and go many times during the next two or three years

The sores in the mouth and on the private parts and the rash on warm, moist parts of the body (between the buttocks under the arms and under a woman s breasts) are full of germs and are very dangerous to anyone who touches them Sexual intercourse and kissing are sure to spread the disease in this stage

The signs of syphilis in this secondary stage will disappear, finally, EVEN WITHOUT TREATMENT Once more the patient thinks he is cured Years later, all kinds of things may happen very serious in nature It is in this stage that the disease so often cripples people physically and mentally

Remember that no doctor looking at a chancre, can be sure that such sore is or is not the sore of syphilis, despite what you may have been told to the contrary In many cases, blood tests are of no use until from two to four weeks have passed There is only one absolutely certain way of making an early certain diagnosis of syphilis if it is too early for a positive blood test That is to look at the fluid from your sore under a special microscope More than one examination may be needed before the germs can be found This test is very important because neither the patient nor the sore should EVER be treated for syphilis until it is proved that the patient has syphilis and it may be dangerous to wait for blood tests to become positive Blood tests should always be made at the same time however, because it *helps the doctor to know* whether the blood is positive or negative at the beginning

Syphilis Can Be Cured

Syphilis is easiest to cure in the first stage harder to cure in the second stage and hardest to cure and many times incurable in the third stage The right kind of treatment in any stage will keep the disease from doing any more harm but some of the damage caused by syphilis in the third stage can NEVER BE REPAIRED

The treatment of syphilis depends upon the extent of the disease and the condition of the patient when the treatment is begun Treatment of the sore alone (burning the chancre *off)* will NEVER cure syphilis The so called first and second stages are treated in somewhat

White Lotion

Zn sulfate
Potass sulfurata aa 4%
Aqua dist q.s

Oily Spray

Menthol	gr 1 ss
Camphor	gr ¾
Eucalyptol	gr 1 ss
Liq petrolat	qs Oz I

Oil of Rose Compound

1% Cocaine alkaloid in liq petrol
1 drop of oil of rose geranium

Sedative Cough Mixture

Codeine	gr viii
Dover's powders	gr viii
Acetylsal acid	gr XL
Syr to taste qs OZ IV	

Sig 1 teaspoonful q 3 hours

Bronchitis—Cough

Codeine PO₄	0 25
Ephedrine HCl	0 25
Potass Iodide	5 0
Elix phenobarb	60 0

Nervousness

Chloral hydrate	10 0
Elix triple brom	120 0

Sig 1 teaspoonful p r.n

Nervous Stomach

Na phenobarbital	2 0
Tinct belladonna	16 0
Elix Lact pepsin	120 0

Sig 1 teaspoonful t i d a c in half glass water

Antiseptic Nasal Wash

Na Bicarbonate	
Na Biborate aa	Oz I
Na Cl	Oz II

Sig Dissolve 1 teaspoon in ½ pt water

Dermatophytosis

Salicylic acid	3 0
Benzoic acid	6 0
Iodine crystals	2 0
Alcohol 95% ad	100 0

Sig Apply locally to the parts once nightly for one week

ABC Gargle Powder

Alum
Borax
Potass chlorate aa

Sig 1 teaspoon dissolved in ½ glass of water

Antispasmodic Ureteral Enterospasm

Benzedrine SO₄	gr [illegible]
Phenobarbital	gr ¼
Atropine	gr [illegible]
Pulvis digest comp q s	gr V
Fac caps # XX tales doses	

Sig Cap i t i d a.c.

Tonic

Tr nux vom U S P	8 c c.
Tr gent comp U S P	30 c c
Water to	120 c c

Sig 1 teaspoon in water a c

Nausea—Vomiting

Tinc Belladonna	15 0
Elix NaBr	180 0

Sig 1 teaspoonful a.c

Diarrhea

Bis subnitrate	dr viii
Paregoric	Oz iii

Sig 1 teaspoonful q 2 hours

Toothache Drops

Iodine	Oz I
Menthol	gr v
Chloroform	Dr ii
Tinct aconite	Dr i

Mild Acne Lotion

Salicylic acid	
Resorcin	aa 2%
Alcohol 40% qs	Oz II

Sig Locally b i d.

Chronic Tonsillitis

Iodine	gr VI
K Iodide	gr XXV
Ol Menth Piperitae	gtt. X
Glycerin ad	Oz VI

Sig Apply to back of throat

Dusting Powder—Epidermophytosis

Salicylic acid	5 gm
Menthol	2 gm
Camphor	8 gm
Boric acid	50 gm
Starch	35 gm

Tonic

Tinct nux vomica	dr vi
Tinct capsicum	dr i
Dil HCl (optional)	Oz ss
Tinct gen comp qs	Oz iii

Sig 1 teaspoonful in water a c

P M C Douche

Oil of peppermint	6 c c
Liq phenol	12 c c
Alum	30 gm
Boric acid	120 gm

Sig 2 teaspoons to 1 qt water

Sippy Powders

Day

Calcii carbonate	0 6 gm
Sodii bicarbonate	2 0 gm

Sig 1 level teaspoonful Dispense 240–480 gm

Night

Magnesia (calcined)	0 6 gm
Sodii bicarbonate	0 6 gm

Sig 1 level teaspoonful Dispense 120–240 gm

Arthritis Mixture #1

Sod Salicylate	gr x
Sod bicarbonate	gr x

Sig 1 of each q 4 hours

P C G Mixture

Phenol	1 0 c c
Chloretone	1 0 gm
Guaiacol	9 0 c c
Olive oil	180 0 c c

Sig Instill into bladder 15–30 c c

Arthritis Mixture #2

Potass Iodide	dram I
Tinct colchicum	dram IV
Elix Na Salicyl q s	oz IV

Iron Capsules

Iron and ammonium citrate gr vii ss

Iron solution

Iron and ammonium citrate	25 0
Syrup of orange	25 0
Aqua dist q s ad	120 0

Stomach Mixture

Magnesium Oxide	15 0
Bis Subcarbonate	20 0
Na Bicarbonate	30 0
Calcium carbonate	30 0
Oil of peppermint	065

Hypertension Headache

Sodium nitrite	0 065
Caff citrate	0 3
Amidopyrine	0 6
Na Bicarbonate	0 3

Sig Fac in caps—take one B i d

Schultle Mixture (Pruritus)

Zn oxide	Oz II
Starch	O II
Glycerin	Oz IV
Salicylic acid	dr II
Lime water q s ad	1 pint

Ringworm Ung

Salicylic acid	1 2
Ung sulfur q s	30 0

Ung Sulfur Comp

Ppt sulfur 6%
Salicylic acid 3%
Vaseline q s

Nose Drops #1

Neosilvol 20%
Ephedrine SO_4 3% aa dram ii

A and C Oil

Atropine Alkaloid 1%
Cocaine Alkaloid 4%
Castor Oil q s

Cough Expectorant

Ammonium chloride	10 0
Elix Terp Hydr	110 0

A P C Tablets

Aspirin	gr iii ss
Phenacetin	gr ii ss
Caffeine	gr ss

Hair Tonic

Resorcin	gr LX
Bichlor of Hg	gr ss
Alcohol	Oz IV
Alcohol dist q s ad	Oz VI

Scalp Remedy

Salicylic acid	gr XX
Ppt sulfur	dr I
Oil of lemon	dr ss
Cold cream	Oz 1

Whitfield s Ointment

Salicylic acid 6%
Benzoic acid 12%
Vaseline q s

Whitfield s

½ strength

Poison Ivy

Zinc sulfate 3%
Calamine lotion comp

Gast o-Int i nal Tract		
For c llectio of gastr c j ice	Alcoh l U S P	50 c c of a 7% sol t on
	Histamine ph phate U S P	0 5 mgm subc tan ously
For X ray vis-u lizat on	Bari m sulf te U S P	100–150 gm o ally
Kid y F nc t	Phenol ulfonphth le n U S P	1 c c of 0 6% s l tion IM o IV
L ver F ti	B omsulf l N N R	5 mg per kg body w ght IV in 5% sol t o
	Iod phthal sol ble U S P	4 gm orally or 3–3.5 gm *in 24 28 c c f eshly* dist lled ste il w ter IV
	Ph ltetr chlo phtha lein N N R	50–400 mg of disod um lt IV
	Phentet othal i so d um N N R	4 gm orally or 40 mg per kg body w ight. i 8% freshly steril ized w ter sol t n IV
	Rose b gal	100 mg in 10 c c st ile norm l lt sol tion IV
Py l gr phy	D od t N N R	7 gm in 20 c c st ile water *IV*
	H ppuran N N R	12 gm lly 12 gm in 25 c c of St ile w ter IV 15% sol t on (teril) for etro-grad adm tr ti n
	Neo-Iopax N N R	15 gm n 20 c c st ile wate IV
	Skiod N N R	330 mg per kg body wt in 20% st ile solut n IV

Chronic Discharging Ear

Tinct Iodine	0 5
Boric acid	4 5
Alcohol	100 0

or

Hydrogen peroxide	10 vols
Alcohol aa O. ss	

Sig Instill gtt X after drying meatus

DOSAGES OF COMMONLY USED DRUGS

Acetylsalicylic acid (aspirin)	0 3 0 6 gm
Alcohol ethyl	1 2 o
Aluminum hydroxide gel	8 20 c c
Ammonium chloride	0 5 1 0 gm
Amphetamine sulphate (Benzedrine)	5 10 mg
Amyl nitrite	0 2 c c ampule
Amytal	0 1-0 3 gm
Antimony and Potassium Tartrate	*0 1 gm in ampul*
Apomorphine hydrochloride	5 mg
Arsphenamine	0.3-0 6 gm
Ascorbic acid (Cevitamic acid)	50 100 mg
Atropine sulfat	0 25-0 50 mg
Barbital	0.3-0 6 gm
Belladonna (Extract)	15 mg
Belladonna (Tincture)	0 6 c c
Bismuth subcarbonate	1-4 gm
Bismuth subsalicylate	0 1 gm
Brewer's Yeast	2-6 tablet
Caffeine and Sodium Benzoate	0 3-0 5 gm
Calcium carbonate	1 2 gm
Calcium chloride	1 gm
Calcium gluconate	1-4 gm
Calcium lactate	0 3 1 0 gm
Calomel	0 1-0 2 gm
Carbon tetrachloride	2 5 c
Cascara sagrada (Fl ext act)	0.3-0 6 gm
Cascara sagrada (Fl extract)	4 8 c c
Chloral hydrate	0 5 1 0 gm
Codeine sulfate	15-60 mg
Colchicine	0 5 mg
Colchicum (Tincture)	2 c c
De hol	0 24 gm
Demerol	0 05-0 010 gm
Digilen	10
Digitalis (Pulv)	0 1 0 5 gm
Digitalis (Tincture)	1 0 c c
Dilantin	0 1 gm
Dilaudid	2-4 mg
Emetine hydrochloride	60 mg
Epinephrine hydrochloride	0 2-0 5 c 1 1000
Ephedrine sulfate	50 mg
Ergot (Fl extract)	2 c c
Ergotamine tartrate (Gynergen)	1 mg oral 0 5 mg hyp
Estradiol Benzoate	1 mg
Estriol	0 06-0 1 mg
Ferrous carbonate	0 3-0 6 gm
Ferrous sulfate	0 3 gm
Hexylresorcinol	0 2 1 0 gm
Histamine phosphate	0 3 mg
Hyoscyamus (Extract)	30 mg
Ipecac (Syrup)	4 16
Iron and ammonium citrate	1 gm
Lugol's solution	0 3 1 0 c
Milk of magnesia	15-45
Magnesium citrate solution	120 180
Magnesium sulfate	30 saturated solution (15 gm)
Mandelic acid	3 gm q i d
Mercupurin	0 5 2.0 c c
Methenamine (Urotropin)	0 5 gm
Morphine sulphate	8 16 mg
Neoarsphenamine	0 3-0 6 gm
Nicotinamide	25 mg
Nicotinic acid	50 100 mg
Nitroglycerin	0.3-0 6 mg
Pantopon	0 0 gm
Paraldehyde	4 30 c c
Pentobarbital (Nembutal)	*0 1 gm*
Phenobarbital	15-90 m
Phenobarbital sodium	0 13 gm
Phenolphthalein	60 mg
Pitressin	0 5-1 0 c c
Potassium bromide	1 0 5 0 gm
Prostigmin	15 mg oral 1 2 mg hypo
Quinacrine hydrochloride	0 1 gm
Quinidine sulfate	0 2-0 5 gm
Quinine Sulfate	0 6 gm
Reduced Iron	0 5 gm
Riboflavin	1 mg
Saccharin	30 mg
Scopolamine hydrobromide	0.3-0 6 mg
Seconal	0 1-0 2 gm
Sodium bromide	0.3 1 0 gm
Sodium chloride	1-4 gm
Sodium salicylate	0 3 1 0 gm
Strychnine sulfate	2 mg
Sulfanilamide	0 5-4 0 gm (See table page 1039)
Sulfapyridine	0.5 2 0 gm (See table page 1039)
Sulfathiazol	0 5 3 0 gm (See table page 1039)
Sulfadiazin	0 5 3 0 gm (See table page 1039)
Syntropan	10 mg
Theobromine sodium salicylate	0 5 gm
Theobromine sodium acetate	0 2 gm
Theophylline ethylenediamin (aminophyllin)	0 2 gm oral 5 50 mg intravenous 0 48 gm intramuscular
Thiamine chloride	5 50 mg
Thyroid (Armour)	*0 015-0 2 gm*
Tincture opii	0 6 c c
Tinctura opii camphorata (Paregoric)	4 8 c c
Totaquin	0 6 gm
Tartar emetic	mg

ACCEPTABLE DRUGS FOR DIAGNOSTIC PURPOSES IN CLINICAL MEDICINE

Body System	Drug	Dose—Administration
Body Cavities		
For X ray visualization purposes	Campiodol emulsion N N R	1 20 c c for retrograde [illegible]ography
	Lipiodol N N R	1 [illegible] d pe[n]ding upon use
	Lipiodol [illegible] rad ol g q [illegible] s e da t N N R	1 2 [illegible] nt [illegible] p n lly
	Lipiodin N N R	20 c [illegible] d p [illegible] d g on u
	Ethyl [illegible] e U S P	10 [illegible] tr [illegible] pinally
Eye		
For dilating pupil to permit retinal exam	Cocaine hydrochloride	1 2 drop 1% solution
	Eucatropine N N R	2 d [illegible] 5 10% solution
	Homatropine HCl N N R	drop 1% solution
For detect[ing] corneal [illegible]	Fluorescein soluble U S P	1 drop 1% solution

Normal Standards

HEMOGLOBIN

Adult male—average 15 6 gm (13 5–19 5), 85 per cent to 110 per cent

Adult female—14 3 gm (11–16 5 gm) 72 per cent to 105 per cent

Children 6 months to 2 years—average 12 2 gm (9 4–15 4) 60%–100%

RED CELLS

(Millions in cubic millimeter)

Adult male—average 5 4 (4 4 to 6 4)
Adult female—average 4 8 (4 07 to 5 55)
Children 1 to 2 years 5 to 6 million
Color index should equal 1 It is computed

$$\frac{\text{Per cent Hemoglobin}}{\text{Per cent R B Cells}}$$

LEUCOCYTES

Total in cubic millimeter—4 000 to 10 000
Differential percentage
- Lymphocytes 20–40 per cent
- Monocytes, 1–3 per cent
- Eosinophiles 1–3 per cent
- Neutrophiles, 60–75 per cent Segmented 55–65 Stab 5 to 10
- Myelocytes less than 1 per cent

Infants and children have more (50 per cent) lymphocytes

BLOOD PLATELETS

150 000 to 350 000 per cubic millimeter

Bleeding time 2 to 5 minutes
Clotting time 2 to 8 minutes
Prothrombin clotting time 10–20 seconds (Quick)

RED CELL FRAGILITY

Beginning hemolysis 0 45 NaCl
Complete hemolysis 0 35 NaCl

CELL DIAMETER

7 5 microns (6 to 9)

CORPUSCULAR VOLUME

Average 42 per cent (36 to 52 per cent)

TOTAL QUANTITY

Plasma—5 per cent of body weight

CEREBROSPINAL FLUID

Water pressure reclining 100 to 200 mm Children 50 to 100

Mercury value × 14 equals the water value
Total volume of spinal fluid 100 to 150 c c
Globulin—a trace not demonstrable by ordinary test
Sugar 0 04 to 0 07 per cent (40–70 mg per 100 c c)
Cells—0 to 4
Chlorides as NaCl 700–750 mg per 100 cc
Total protein 10–35 mg per 100 c c

GASTRIC CONTENTS (ADULTS)

Emptying time usually in four hours always in six hours
Capacity 1 to 1½ liters (33 to 60 ounces)
Quantity in fasting stomach 0 to 50 c c Top limit is 3½ oz
Free hydrochloric acidity Fasting 5 to 30°
After test meal 30 minutes—20 to 60 c c
After histamine chiefly free HCl 40° to 140
Total acidity fasting 15° to 45° Thirty minutes after meal 30°–75°

URINE

Quantity—adult, 1000 to 1500 c c (33 to 60 oz) in 24 hours
Night about one fourth to one half the day quantity
Specific gravity of mixed 24 hour specimen, 1 015 to 1 020
After drinking much water, 1 002
After 12 hour water starvation 1 030 to 1 035
Reaction usually acid sometimes neutral or alkaline Varies with diet
Albumin—25 to 75 mgm per liter, too little to show with ordinary tests
Sugar—0 05 to 0 2 per cent too little to show with ordinary tests
Chlorides—10 to 15 mg in 24 hours varies with diet
Urea—in 24 hours 25 to 40 grams (average 33)
Lead—Less than 0 1 mg excreted in 24 hours
Calcium—0 5 gm

CHAPTER XXI

CLINICAL LABORATORY MEDICINE

By Seward E. Miller

Concentration of Constituents of Normal Persons

Constituent	Phase	Per 100 c c	Milliequivalents per liter	Requirement
		Blood		
Total protein	Serum	6.0–8.0 gm		5 c c clotted blood
Albumin	Serum	3.6–5.4 gm A/G ratio is 1.7:1 to 3:1		10 c c clotted blood
Globulin	Serum	1.5–3.4 gm		4 c c clotted blood
Fibrinogen	Plasma	0.3–0.6 gm		4 c c oxalated blood
N P N	Blood	25–35 mg		5 c c oxalated blood
B U N	Blood	10–15 mg		2 c c oxalated blood
Uric acid	Blood	2–4 mg		5 c c oxalated blood
Creatinine	Blood	1–2 mg		5 c c oxalated blood
Glucose	Blood	80–120 mg (Na fluoride as anti coagulant		5 c c oxalated blood
Amylase	Serum	70–200 units		8 c c clotted blood
Ascorbic acid*	Serum	0.6–2.5 mg		10 c c clotted or oxalated blood
Cholesterol	Serum	160–220 mg		3 c c clotted blood
Sodium	Serum	315–340 mg	137–147 m Eq	5 c c clotted blood
Calcium	Serum	9–11 mg	4.5–5.5 m Eq	8 c c clotted blood
Phosphorus	Serum	*Adults* 2.0–4.0 mg *Infants* 4.0–6.0	0.8–1.45 m Mole 1.3–1.9 m Mole	5 c c clotted blood
Phosphatase alk	Serum	2–4 B units		5 c c clotted blood
Phosphatase acid	Serum	0.5–1.0 units		
Chloride	Serum	425–455 mg	119–128 m Eq	5 c c clotted blood
CO_2 capacity	Plasma	50–70 vol %	22–31 m Mole	10 c c oxalated blood
Oxyhemoglobin	Blood	13–16 gm	18–22 vol % O_2	1 c c oxalated blood
T bilirubin	Serum	0.1–0.8 mg		8 c c clotted blood
Sulfonamides	Blood			1 c c oxalated blood
Na bromide	Serum			8 c c clotted blood
Phenols	Blood	1–2 mg		6 c c oxalated blood
Potassium	Serum	16–22 mg		10 c c clotted blood
Iodine	Plasma	8–16 micrograms		10 c c oxalated blood
		Cerebrospinal Fluid		
Total protein		20–35 mg		5 c c fluid
Glucose		40–70 mg		1 c c fluid
Chloride		425–455 mg	119–128 m Eq	2 c c fluid

* Make an appointment with the Chemical laboratory *before* the blood is collected

Calculation Sodium—1 milliequivalent/liter equals 2.3 mg %
Calcium—1 milliequivalent/liter equals 2.0 mg %
Phosphorus—1 millimol/liter equals 3.1 mg %
CO_2—1 millimol/liter equals 2.24 vol %
Chloride—1 milliequivalent/liter equals 3.55 mg %
(3.55 mg chloride are contained in 5.85 mg NaCl)

Chlorides should be never run on whole blood There is greater accuracy in running the tests on serum

CALCIUM (SERUM)

Normal function
- a Composition of osseous tissues
- b Clotting of blood
- c Contraction of muscles irritability of nerves
- d Affects H ion concentration of blood
- e Influence on allergy

Normal amount 9 to 11 mg per 100 c c or 4 5 to 5 7 m Eq /liter Ordinarily 3 to 5 mg per 100 c c bound to protein Ca falls as the inorganic phosphate rises and Ca rises with the increase of plasma protein

Normal calcium—potassium ratio is 1 2

Low values in
- a 4 mg per 100 c c in hypoparathyroidism (severe)
- b Hyperthyroidism
- c Pellagra
- d Jaundice
- e Colitis
- f Nephritis—Ca drops as PO_4 retention ensues
- g Steatorrhea (adult celiac disease) excessive loss of calcium soaps by the bowel may reduce the serum Ca to well below 7 mg
- h Osteomalacia 2 types
  - 1 Ca little reduced but PO_4 subnormal
  - 2 Ca low and PO_4 low to slightly increased (common)
- i Clinical tetany occurs with values below 7 mg

High values in
- a Hyperparathyroidism—critical level 20 mg /100 c c
- b Hypothyroidism
- c Paget s Disease
- d Arthritis deformans (normal values the rule)
- e *Acromegaly*
- f Occur secondary to increased plasma protein as in multiple myeloma
- g Artificial hypervitaminosis D may push level up to 20 mg for short periods

Normal amount excreted daily—1 gram

Excretion increased in hyperthyroidism (feces) hyperparathyroidism (urine principally) Excretion decreased in hypoparathyroidism rickets

CHOLESTEROL—TOTAL (PLASMA)

Functions Inhibits hemolysis—contributes to cell manufacture—essential to life—cholesterol esters are 75 per cent cholesterol In normal plasma both are present in constant amounts

Normal range Range from 160 to 220 mg per 100 c c for total cholesterol

Low values in
- a Prolongs starvation cachexia scurvy
- b Certain anemias
- c Infections
- d In hyperthyroidism cholesterol falls as the BMR rises
- e Uremia
- f Epileptic attacks

High values in
- a 300 mg /100 c c found in pregnancy, myxedema and the so-called nephrotic syndrome
- b Diabetes
- c Hypothyroidism
- d Pregnancy
- e Chronic tubular and acute nephritis
- f Cholelithiasis obstructive jaundice
- g Schuller Christian syndrome
- h Arteriosclerosis malignancy neurosyphilis
- i Obesity with diabetes or hypertension
- j Ratio of esters to free cholesterol characteristically low in parenchymatous liver disease
- k *Fevers*

CHOLESTEROL ESTERS (PLASMA)

Normal range 110-175 mg per 100 c c (60-80 per cent of total) Increased in Chronic glomerulonephritis nephrosis biliary obstruction Decreased in Acute hepatitis and chronic cirrhosis

CREATININE (BLOOD)

1 Unaffected by age, diet exercise pregnancy Material equally distributed between cells and plasma

2 Normal function
- a End product of creatine metabolism
- b Results from muscular activity

BASAL METABOLIC RATE

	Lower Limit %	Upper Limits %
Normal	minus 10	plus 10
Obesity	minus 14	plus 10
Cardiorenal (without dyspnea)	normal	
Colloid goitre	minus 18	plus 5
Metabolism Raised		
Menses and pregnancy	0	plus 25
Mild exophthalmic goitre	plus 15	plus 30
Moderate exophthalmic goitre	plus 30	plus 50
Severe exophthalmic goitre	plus 50	plus 75
Very severe exophthalmic goitre	over 75	
Pernicious anemia	0	plus 40
Leukemia	plus 20	plus 125
Fevers	plus 5 to 10 for each degree Fahrenheit	
Hyperpituitarism	plus 10	plus 40
Early diabetes	0	plus 20
Cardiac decompensation	plus 25	plus 50
Nephritis without edema	0	plus 30
Metabolism Lowered		
Myxedema and cretinism	minus 40	minus 15
Prolonged undernutrition	minus 30	minus 10
Frolich's syndrome	minus 25	0
Simmonds's cachexia	minus 50	minus 10
Addison's disease	minus 40	0
Low heart rates in healthy	minus 20	0
Nephritis	minus 40	0

SEDIMENTATION RATE

Normal

a Less than 6 mm in 45 minutes
b Less than 12 mm in 90 minutes
c Less than 18 mm in 2½ hours
d Less than 24 mm in 4 hours

Accelerated in

a Premenstrual period pregnancy
b Inflammation infection malignancy
c Hyperthyroidism
d Diabetes in old age

Blood Chemical Values in Health and Disease—Laboratory Interpretation

Note All values in mg per 100 c c unless otherwise specified m Eq signifies milli equivalents per liter

AMINO ACIDS (SERUM)

Normal range 5–8 Commonly increased in acute yellow atrophy Commonly decreased in nephrosis and acute infections

BILIRUBIN (SERUM)

Normal range 0 1–0 8 Commonly increased in Biliary obstruction toxic hepatitis hemolytic anemia pernicious anemia Commonly decreased in Iron deficiency anemia

CARBON DIOXIDE COMBINING POWER (PLASMA)

Normal range 40–50 vol per cent (children), 50–70 vol per cent in adults Increased in Alkalosis, pyloric obstruction ingestion of bicarbonate, hyperventilation Decreased in Acidosis diabetic, renal Dehydration, starvation, Emphysema

CHLORIDES (PLASMA)

Normal range 119 to 128 m Eq per liter or 425–455 mg per 100 c c of blood Decreased in starvation or heat exhaustion A drop of 3 m Eq /liter in alkaline tide due to gastric acid secretion

Pyloric obstruction with repeated vomiting loss of gastric HCl may reduce serum chloride to less than half its normal value

Diabetic ketosis—despite accompanying dehydration the values may fall to 96 m Eq /liter as the combined result of vomiting diuresis, accumulation of oxybutyrate and acidosis

In pneumonia there may be a drop to 90 m Eq /liter for which reason some clinicians suggest giving salt up to the point of edema

In eclampsia low chlorides common, also in TBC pneumonia, HgCl poison

High values in

a Values up to 130 m Eq /liter may be induced by giving 40 gm of salt a day
b Diarrhea—slight increase or normal
c Preceding diuresis—may rise to 140 m Eq /liter
d Acute or chronic glomerulonephritis—slight increase
e Gouty nephritis—slight increase
f Addison s Disease
g Fevers
h Pneumonia
i Gastrointestinal disturbance associated with vomiting

Normal amount in the urine 10 to 15 gm daily

Increased by drinking large amounts of water decreased by physical exercise

Function of Chlorides

a) Maintain osmotic and base equilibrium of the blood
b) Contribution to the hydrochloric acid of the gastric juice
c) Balance between sodium potassium and calcium for normal heart action

Chlorides should be never run on whole blood There is greater accuracy in running the tests on serum

CALCIUM (SERUM)

Normal function
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- f Cholelithiasis obstructive jaundice
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CREATININE (BLOOD)

1 Unaffected by age diet exercise pregnancy Material equally distributed between cells and plasma

2 Normal function
- a End product of creatine metabolism
- b Results *from muscular activity*

3 Normal range 1 to 2 mg per cent Normal urinary excretion is 1 0 to 1 25 gm per day
4 Increased in
   a Increased tissue catabolism
   b Diabetes
   c Fevers (typhoid, tetanus, typhus, pneumonia)
   d Values up to 5 0 mg per 100 c c are common in chronic nephritis Above 10 mg the prognosis ordinarily is very poor and a value approaching 18 mg warns of imminent death
   e In urologic conditions producing obstruction low in the urinary tract, the creatinine tends to be slightly elevated, *even when the blood urea nitrogen is* high This point is of diagnostic importance in prostatism, urethral stricture, and carcinoma of the bladder
5 Decreased in
   a Muscular atrophy and weakness
   b Advanced kidney lesions
   c Anemia
   d Paralysis
6 Creatinine index Index equals the milligrams of creatinine excreted per day divided by the body weight in kilograms Value from 20-26 for normal men 14-22 for women Its value depends on the muscular development of the individual and it may be higher in athletic women than in an obese man of poor musclar build

CREATINE

1 Normal amount in urine is small
2 Increased in
   a Graves disease
   b Childrens urines
   c Pregnancy
   d Addison's disease
   e Malnutrition and emaciation
3 Decreased in hypothyroidism
4 Creatine tolerance test—increased in Graves' disease, decreased in muscular diseases
5 Creatine index
   a Ratio creatine to creatinine
   b Normal 1 10
   c Decreased in hypothyroidism (1 15 or 20) and muscular diseases
   d Increased in hypothyroidism 1 8 to 1 4

FIBRINOGEN (PLASMA)

Normal value 300-600 mg per 100 c c (0 3 to 0 6 gm) Commonly increased in (a) acute and chronic infections, (b) tissue necrosis Commonly decreased in (a) acute yellow atrophy, (b) chloroform and phosphorus poisoning

SUGAR (FRESH PLASMA OR SERUM PREFERABLE FROM CHEMICAL POINT OF VIEW)

Normal amount 80 to 120 mg per 100 c c fasting Over 130 mg abnormal
Increased in
   a Diabetes or pancreatic disease
   b Hyperthyroidism (after meals—common)
   c Severe nephritis
   d Some liver disturbances
   e Obesity
   f Gastritis
   g Excitement — fear — cold — asphyxia —after brain injury These are all reactions of the sympathetic nervous system
   h Venous blood lower than arterial in the normal post absorptive state The reverse is true in diabetes
Decreased in
   a Starvation
   b Hypopituitarism
   c Exhaustion
   d Addisons disease
   e Acute yellow atrophy of the liver
   f Severe hypoglycemia
   g Tumor of pancreas (islet tumors)
   h Hyperinsulinism
   i Hypothyroidism
   j Insulin shock
   k Severe muscular activity
Not normally found in urine
Glycosuria occurs
   a With blood sugar above the tolerance point (160-180 mg)
   b Low kidney threshold (renal glycosuria)
   c Diabetes
   d Pregnancy
   e After adrenalin injection

f Hyperpituitarism
g Nicotine poisoning

SUGAR TOLERANCE

Normal value Ingestion of 100 gm of glucose without glycosuria and rise of only 60 to 70 mg per cent Return to fasting level in two hours

Increased flattened curve in
a Young children
b Hypothyroidism
c Hyperinsulinism
d Hypopituitarism
e Addison s disease

Decreased (extreme rise and delayed return) in
a Diabetes
b Hypopituitarism
c Hyperthyroidism
d Pregnancy

IODINE (BLOOD)

Normal function in manufacture of the thyroid hormone

Normal value 8–16 micrograms per 100 c c

Low values 0 5 to 6 5 micrograms per 100 c c are encountered in myxedema and cretinism and in polyglandular syndromes like Simmond s cachexia that involve the thyroid gland

High values These are found in hyper thyroidism in toxic nodular goitre and some cases of acromegaly Such values range from 16 to 36 micrograms per 100 c c and possibly higher depending upon the severity of the disease Long standing cases of so-called hyperthyroidism however may show normal iodine values presumably because the thyroid stores of iodine have become exhausted

ICTERUS INDEX (SERUM)

Normal value 0 to 6 units

Increased in Hemolytic anemia—pernicious anemia biliary obstruction hepatitis and cirrhosis

Decreased Anemia of iron deficiency

HYDROGEN ION CONCENTRATION

Normal mechanism (a) maintenance of slight blood alkalinity (b) system of buffer substances

Normal pH of blood is 7 3 to 7 5 Normal pH of urine is 5 8 to 6 0

Increased in alkalosis

Decreased in acidosis

NON PROTEIN NITROGEN

Normal range Between 25 and 35 mg per 100 c c rarely to 40 mg Represents urea amino acids uric acid creatine, creatinine N P N concentration is higher in the cor puscles In the plasma it is only 18 to 30 mg, i e, twice the blood urea nitrogen It repre sents the balance between protein catabolism and urinary elimination Considerable diurnal variation makes it necessary to get fasting values

Low values in
a Starvation and cachexia
b Normal pregnancy

Increased in
a Hypothyroidism
b Hypo adrenalism
c Hyperpituitarism
d Azotemia of nephritis—100 to 200 mg per 100 c c in terminal or acute ex acerbations
e Mercury and uranium poisoning
f Dehydration with heat cramps after burns X ray necrosis hyperthyroid crises hyperparathyroidism, advanced hepatic cirrhosis G I vomiting from obstruction after severe diarrhea as in cholera
g Chronic passive congestion surgical shock severe fevers acute infections
h Diabetic coma
i Uncomplicated gout
j Salt lack in Addisonian crises
k Azotemia accompanying hepato-renal death (Weil s disease)
l Impaired renal efficiency

BLOOD UREA NITROGEN

Normal function (a) waste product of pro tein metabolism (b) produced chiefly in the liver

Normal amount in blood 10–15 mg per 100 c c. 9–23 mg rarely and due to changes in the nitrogen metabolism

Increased in
a Severe kidney deficiency
b Malignant disease
c Pneumonia

d Intestinal or prostatic obstruction
e *Lead poisoning and granular kidney*
f Hyperparathyroidism
g Adrenal deficiency
h Dehydration
i Renal insufficiency due to congestive *heart failure*

Decreased in
a Pregnancy and eclampsia
b Possibly hepatic insufficiency
c Found after diuresis as urea is swept out of the body with body water Because a high carbohydrate diet spares protein metabolism, the normal range may drop 40 per cent when carbohydrates are forced

Urea clearance decreased in
a Renal insufficiency
b Addison s disease
c Hyperparathyroidism

Tests Used

I Van Slyke Urea Clearance Normal over 40 c c of blood cleared per minute

II Mosenthal Index—the ratio of B U N to the total N P N multiplied by 100 Upper limit of normal is 44 Values above 80 *suggest Bright s disease and impending* uremia A normal ratio with a high N P N (total) suggests that primary renal insufficiency is not present

PLASMA PROTEINS

Normal values 6 5 to 7 5 gm per 100 c c (rarely 6 0 to 8 0 gm)

Divided
Albumin 3 6 to 5 4 gm
Globulin 1 5 to 3 4 gm
Fibrinogen 0 3 to 0 6 gm
Albumin globulin ratio is 1 7 1 to 3 1

Low values in (total protein) Nephrotic syndrome, Bright s disease malnutrition infections, cirrhosis of the liver

Edema—critical value heralding onset is below 5 0 gm total protein and 2 5 gm albumin

High values in Dehydration following vomiting and diarrhea (cholera) Multiple myeloma (12 gm plus) Lymphogranuloma venereum (generally) Hepatic inflammation —globulin fraction high It usually falls after extensive liver damage Kala Azar—high globulin values

BLOOD URIC ACID (USE SERUM)

Normal function The end product of purine oxidation

Normal amount in blood 2 0 to 4 0 mg per 100 c c (blood), 3 0 to 5 0 mg per 100 c c (serum)

Repeat when over 6 0 even though no indication of gout

Increased in
a Fasting or after eating sweetbreads
b Gout—5 to 11 mg per 100 c c
c Moderate rise in Leucemia—Advanced chronic nephritis—polycythemia
d Temporary rise in pneumonia and severe exercise
e Decreased kidney permeability
f Severe fevers
g Eczema
h Starvation
i Hypopituitarism and hypo adrenia

Decreased in
a Normal pregnancy
b After administration of salicylates or cinchophen
c Diuresis following calcium chloride administration

Normal amount in urine, 0 7 gm daily

Increased in
a Gout
b Leucemia
c After administration of cinchophen
d Hyperpituitarism

Decreased after diet low in purine bodies

PIGMENTS (PLASMA BILIRUBIN)

Normal Range from 0 1 to 0 8 mg per 100 c c corresponding to an icteric index of less than 6 One Van den Burgh unit equals 0 5 mg per cent bilirubin

High In hemolytic anemia the increase in bilirubin varies with the disease In obstructive jaundice or acute yellow atrophy extremely high values are found over 40 mg per 100 c c corresponding to an icteric index well over 100 As a rough approximation, skin pigmentation occurs at 4 Van den Burgh units equalling 2 mg per 100 c c or an icteric index of 20

Qualitative Van den Burgh Test This test is now thought by many to be of dubious value in most cases It rests on the principle

that normal blood plasma contains colloidal bilirubin whereas normal bile contains the pigment after detachment from its colloid carrier The qualitative test should not be confused with the quantitative procedure used to determine total bilirubin Obstruction due to stone in the common bile duct is rarely complete when subjected to such quantitative evaluation Cancerous obstruction is frequently complete

Pigment Metabolism in Jaundice

Plasma

	Colloidal Bilirubin	Bile Pigment	Urobilinogen
Normal	Plus 1	0	0–trace
Hemolytic jaundice	Plus 4	0	Trace
Cri — mpl at n	Plus 4	1	Trace
Hepatogenous jaundice	Plus 1?		
Complete obstruction of common bile duct	Plus 1	4	

Urine (24 hour period)

	Bile Pigment	Urobilinogen	Urobilin	Combined Urobilin and Urobilinogen
Normal	0	Pl t	Plus 1	0–4 mg
Hemolytic jaundice	0	Slight trace		1 10 mg
Cirrhosis—complication	Plus 1	Plus 4	Plus 3	10–300 mg
Hepatogenous jaundice	Plus 3	Plus 2	Plus 2–4	4 00 mg
Complete bile duct	Plus 4	0	0	0

E pt n alcoholic stool per day

Stool (24 hour period)

	Urobilin	Combined Urobilin and Urobilinogen
Normal	Plus 3	40–250 mg
Hemolytic jaundice	Plus 4	300–1 800 mg
Hepatogenous jaundice	Plus 2	10–300 mg
Complete obstruction of common bile duct	0	0–5 mg

INORGANIC PHOSPHORUS

Normal function

a Contributes to bony structure

b Contraction of muscles

c Buffer in pH of blood influencing the cell permeability

d Aids in action of digestive juices and insulin

Normal values Adult s serum—2 to 4 mg per 100 c c infant s serum—4 to 6 mg per 100 c c

Low values in Hyperparathyroidism ostoe malacia rickets

Insulin and adrenalin causes a fall

High values in After major fractures hypoparathyroidism ingestion of excessive amounts of Vitamin D after administration of pituitrin terminal nephritis—condition critical at 8 mg /100 c c with death expected at 20 mg /100 c c

It is interesting that despite the marked clinical correlation of high plasma phosphate with low serum calcium the onset of tetany is not directly related to the phosphate except through pH and calcium There is scientific evidence that the local concentration of carbon dioxide in the tissues not the calcium nor the reaction is the final precipitating factor in tetany (1)

Blood Findings in Tetany

Type	Serum CA	Blood Bicarbonate	Plasma pH	Serum Phosphate P
Parathyroid	Low	Normal	Normal ?	Increased
Gastric	Normal	Increased	Alkaline	Normal
Hyperpnoeic	Normal	Low	Alkal	Normal
Alkalin	Normal	Increased	Alkalin	Normal
Infantile	Low	Normal	Normal	Increased ?

PHOSPHATASE ALKALINE (SERUM)

Function Hydrolyzes phosphoric esters Results in precipitation of calcium salts as bone Indicates capacity of bone for cellular activity

Normal range 2 0 to 4 0 units per 100 c c (Bodansky units) 0 2 to 0 3 units per 100 c c (Kay)

Increased in Rickets Paget s disease hyperparathyroidism biliary obstruction myositis ossificans carcinoma metastasis to bone hyperpituitarism chronic arthritis

Decreased in Malnutrition anemia senility

PHOSPHATASE ACID (SERUM)

Normal 0 5 to 1 0 units

Patients with carcinoma of the prostate gland who have bone metastases show a marked increase in their acid phosphatase This test is used increasingly in cases of carcinoma or suspected carcinoma of the prostate to indicate whether or not metastases are present in order to determine the best type of therapy to be instituted

POTASSIUM

Normal function

a Acid base equilibrium of the blood

b Osmotic pressure

c Affects permeability of the capillaries
d Vagotonic

Normal amount in blood 16–22 mg per cent of serum

Increased in Tetany, adrenal insufficiency, pneumonia, uremia

Decreased in anemia

Normal amount in urine ranges from 1 to 3 gm daily

SODIUM (SERUM)

Normal function

a Osmotic equilibrium
b Acid base balance
c Sympatheticotonic
d Aids the heart action

Normal range 315 to 340 mg per cent or 137 to 147 m Eq /liter

Increased in Dehydration

Decreased in Addison's disease terminal nephritis diarrhea, profuse vomiting from gastro intestinal obstruction diabetes

PANCREATIC ENZYME TESTS

Normal values In patients without known abdominal disease—Lipase, 0–1 5 c c 20/N NaOH per c c serum amylase 70–200 units is the normal value

In pancreatitis The serum lipase values are seen up to 12 c c of 20/N NaOH per c c of serum The serum amylase has reached 1600 units in some cases Increased values may persist for many months when the inflammation becomes chronic but remains active

In carcinoma of the pancreas Elevated values for enzymes in serum occur in occasional cases of carcinoma in which the body and tail of the organ are chiefly involved In such cases elevated values are of greater importance than when carcinoma is in the head of the pancreas since obstructive jaundice and a palpable gall bladder are absent in carcinoma confined to the body and the tail

The serum lipase determination gives greater information It is elevated in 40 5 per cent of the cases Values are normal in disease (malignant) of the biliary tract

Minimal Clinical Laboratory Blood Chemistry Diagnostic Aids to Order

A full blood chemical examination involves considerable expense and the routine performance of needless tests indicates a lack of skillful observation and thinking dulls clinical acumen and wastes time and materials

1 *Blood Sugar Determinations* Order only in cases of diabetes or suggestive subjective symptoms with obesity, arteriosclerosis or gallbladder disease Suspected hypoglycemia is also an indication for the test

2 *Sugar Tolerance Tests* This is unnecessary when the fasting blood sugar is above 0 15 per cent, i e 150 mg per cent

3 *Carbon Dioxide Combining Power of the Plasma* Indicated in
   a Diabetic patients with much diacetic acid in the urine
   b Uremic patients with much nitrogen retention
   c Patients showing severe toxic symptoms associated with marked disturbance of gastrointestinal motility, such as occurs in protracted vomiting, peritonitis distension, or probable obstruction

4 *Blood Urea* Blood urea determinations are of value in cases of suspected renal disease and the toxemias of pregnancy, intestinal or prostatic obstruction and adrenal deficiency

5 *Blood Chlorides* These determinations are of value in dehydration heat cramps heat exhaustion, prolonged vomiting and in Addison s disease They are of great value in extensive burns

6 *Blood Creatinine* Do not ask for blood creatinine unless the urea nitrogen is over 30 It should then be done as a routine

7 *Blood Urea—Non Protein Nitrogen* Do not ask for both they have much the same significance The blood urea nitrogen test is preferable

8 *Blood Uric Acid* Order this only in cases of gout or suspected gout Renal impairment detracts from its diagnostic value

9 *Icterus Index* Order an icterus index only in cases of jaundice suspected jaundice or in anemia

10 *Blood Calcium* Ask for blood calcium determinations only in bone softening pontaneous fracture generalized os

teitis due to hyperparathyroidism renal calculi and in tetany of unknown origin

11 *Inorganic Phosphorus* Order only when practicable in cases of rickets or infantile tetany

12 *Blood Cholesterol* Ask for this test only to confirm a diagnosis of hypo- or hyperthyroidism myxedema or nephrosis or to determine the severity of diabetes Rule out other states in which it is increased (See page 1109)

13 *Serum Albumins and Serum Globulin* It has been customary in the past to place great emphasis upon the ratio of albumin to globulin Since the physiological and clinical consequences of disturbances in the serum proteins depend *upon the actual concentrations of the* albumin and globulin fractions emphasis should be placed on these rather than their ratio Abnormalities in the albumin fraction always occur in the direction of a decrease whereas changes in the globulin fraction are associated with an increase in these proteins This test should be ordered in cases of nephrosis in suspected hypoproteinemia and in cases of idiopathic edema liver disease multiple myeloma leprosy kala azar Boeck s sarcoid and lymphogranuloma inguinale

14 *Acid and Alkaline Phosphatase* This test should be ordered in cases of carcinoma or suspected carcinoma of the prostate gland to determine the presence of metastases

Kidney Function Tests

ALBUMIN

Normal urine has too small an amount to be detected by ordinary tests

Increased in

1 Affections causing increased kidney permeability nephritis and nephrosis
2 Accidental admixture of blood or inflammatory exudates
3 After consumption of large amounts of protein
4 Postural or orthostatic albuminuria appearing during exercise
5 Hypothyroidism
6 Hyperparathyroidism
7 Addison s disease

ACETONE BODIES

Normal amount in blood 3 mg per cent
Normal amount in urine 3 to 15 mg daily
Increased in

a Diabetes and acidosis
b On a carbohydrate free diet
c Toxemias of pregnancy eclampsia

CONCENTRATION TESTS

1 Have patient void and discard the first specimen in the morning

2 Collect specimens in separate bottles every two hours until 6 o clock in the evening

3 Collect all the urine from 6 o clock up to and including the first specimen voided the following morning

4 Send to laboratory for specific gravity determination

I (Sodeman Pituitary Extract Concentration Test)

The advantages of this test is that it requires no preparation of the patient At a convenient time 0 5 c c of pituitary extract (obstetrical) is administered subcutaneously urine samples are collected every half hour for three or more hours A normal response is a specific gravity of 1 020 or greater In extensive kidney disease inability to concentrate above 1 014 is evident In diabetes insipidus the kidneys have a normal concentrating ability following the use of pituitary extract but are unable to concentrate following the restriction of fluids overnight (2)

II (Lashmet Newburg Test)

1 After supper give no liquid or food until 10 00 A M next morning

2 Urine specimens as follows 8 00 A M – 9 00 A M –10 00 A M

3 Record amount and specific gravity of each specimen

4 Failure of concentration to more than 1 016 is significant evidence of lowered kidney function

5 This test is a valuable test of kidney function but demands cooperation on the part of the patient and the hospital staff Both should be carefully instructed

III Phenolsulphonthalein Test

1 Give the patient two glasses of water to promote the secretion of urine

2 Twenty minutes later have the patient empty his bladder and discard the urine Then, with a tuberculin syringe, inject exactly 1 c c or 6 mgm of the sterile phenolsulphonthalein solution intravenously

3 Exactly 15 minutes after injecting the dye have the patient empty his bladder and save the urine

4 Exactly one hour later and again two hours later *after injecting the dye*, have the patient empty his bladder and save all urines in separate containers

5 All three specimens are sent to the laboratory properly labelled

Interpretation An excretion of less than 25 per cent in fifteen minutes or of less than from 60 to 75 per cent in two hours is considered evidence of impaired renal function The test is of no value if the drug is injected subcutaneously in an edematous patient

IV Urea Clearance Test

1 The patient is allowed to eat an ordinary breakfast and is given two additional glasses of water either before or immediately after the meal

2 Following this the patient should empty his bladder completely Discard the specimen and record the exact time when the patient finished voiding This marks the beginning of Period One

3 At the end of approximately one hour the bladder is completely emptied again and the time recorded exactly This marks the end of Period One

4 Within about five minutes withdraw 5 c.c of blood place it in a vial with oxalate for a blood urea nitrogen determination

5 At the end of approximately two hours from the beginning of Period One the bladder is again completely emptied and the time recorded carefully This ends Period Two

6 Send the blood and the two urine samples to the laboratory with a properly filled out request form labelled Urea Clearance Test The exact times of the beginning and the endings of Periods One and Two must be recorded on this sheet This is absolutely necessary in order to calculate the test

Amounts below 40 c c of blood cleared per minute is considered as an indication of renal disability

V Fischberg Renal Function Tests

1 The normal usual evening meal with the usual fluids before 6 P M

2 No fluids after this time until the test is completed

3 Discard all urine specimens passed during the night and evening

4 Have the patient empty his bladder upon awakening and save this specimen label it No 1

5 Have the patient stay in bed one hour later have him again empty his bladder completely label this specimen No 2 The patient may now get out of bed and be up and around for one hour

6 Again have the patient empty his bladder completely and label this specimen No 3

7 Send all specimens to the laboratory with a request form marked 'Fischberg Test'

Interpretation Normally the specific gravity should be above 1 025 Renal insufficiency is indicated if the specific gravity is between 1 010 and 1 020 Should the maximal reading be around 1 020, make an analysis The test is of no value in the presence of congestive heart failure or if edema from any other cause is being evacuated The maximum specific gravity obtainable in severe renal failure is 1 007 the specific gravity of protein free blood plasma, but Fischberg says that under appropriate conditions he has never seen a patient with severe renal disease but who couldn t reach at least 1 010 *Albumen correction* Subtract 0 003 from the observed specific gravity for each gram of albumen per 100 c c of urine

VI Glucose Tolerance Tests

It is suggested that the Exton and Rose Divided One Hour Test be run routinely 100 grams of glucose are dissolved in 600 c c of water and flavored with lemon juice This is then divided into two equal portions of 300 c c each

1 Collect a fasting blood sample and a fasting urine specimen Then give one of the 300 c c portions of glucose

2 Thirty minutes later collect a second

sample of blood and give the second portion of glucose

3 Thirty minutes later collect a third sample of blood and a second sample of urine

4 One hour later collect a third urine sample if desired but this is not necessary

5 Send the two urine samples and the three blood samples to the laboratory

Interpretation The *fasting sugar* should be under 90 mg per cent

The *half hour blood sugar sample* should be under 142 mg per cent

The *one hour blood sugar sample* should be under 158 mg per cent

Owing to the so-called Hamman Hirschmann effect the one hour reading in non diabetics is usually lower than the half hour reading A value of 180 mg per cent or over for the one hour reading is almost certain evidence of diabetes mellitus (3)

Liver Function Tests

WHICH TESTS ARE USEFUL?

In the differentiation between obstructive and parenchymatous jaundice less sensitive liver function tests are indicated i e tests which give positive results only when there is more *severe damage to the liver parenchyma* In patients without jaundice one is interested in discovering slight disorders of liver function and for such the more sensitive liver function tests are required In cases of prolonged obstructive jaundice owing to the presence of secondary hepatitis the differential diagnosis may be impossible with any type of liver function test A correct diagnosis can be made in the majority of cases of jaundice by a good history careful physical examination and simple qualitative urinary tests In the incipient and recovery stages of parenchymatous jaundice *the urine contains bilirubin and much* urobilinogen but only little urobilinogen in the fully advanced stage

One of the commonest problems encountered in patients with jaundice is whether the hepatic disease is due to common duct obstruction or to intrinsic hepatocellular disease The most valuable laboratory procedures in the differentiation between these two conditions are the simultaneous and repeated (1) examination of the stool for the presence of bile (2) the estimation of the urobilinogen excretion and (3) the determination of the icterus index

BILIRUBIN IN THE STOOL

The color of the stool is an adequate index of its bilirubin content and as the amount of bilirubin decreases the color first becomes tan then yellow and finally clay colored when completely free of bile Common duct stone *seldom produces a persistent complete biliary* obstruction and repeated stool examinations in such cases will show fluctuations in the bilirubin content which are reflected by changes in color Urinary urobilinogen excretion also fluctuates with the intermittent bile excretion and gives useful confirmatory evidence of the nature of the obstruction Once biliary obstruction due to neoplasms has developed it is complete and persistent and the stools remain completely acholic and show no fluctuations in color Hepatocellular disease frequently produces a marked decrease in the amount of bile excreted into the intestine and the stools may be clay colored for long periods Completely acholic stools in toxic hepatitis are seldom persistent and usually transient fluctuations in the bile content are seen In contrast to the finding with stone the urobilinogen excretion in the urine is much greater in hepatocellular disease because of the impaired excretory function of the hepatic parenchyma

UROBILINOGEN EXCRETION

Urobilinogen is formed in the intestine by the bacterial decomposition of bilirubin *Some of the urobilinogen is absorbed through* the intestinal wall and appears in the blood where it is excreted by the liver and appears in the bile Small amounts pass through the kidney and normally 0 5 to 2 0 mg appear in the urine in a *twenty four hour period*

Technique of the Test

To 2 c c of freshly voided urine add 5 to 8 drops of Ehrlich s modified aldehyde reagent (para-dimethyl amino benzaldehyde 0 7 gm concentrated hydrochloric acid 150 0 c c distilled water 100 c c) To this is now added 4 to 5 c c of a saturated aqueous solution of sodium acetate A color varying from pink to deep red indicates urobilinogen Normal

urine will produce only a weak pink color at the most The urine must be cooled to room temperature or lower before the test is run Quantitative determinations carried out on 24 hour specimens are best By comparing the color obtained with phenolsulfonthalein standards and applying the formula developed by Watson (Archives of Int Med 59 522 1937) the urobilinogen excretion per day can be carried out and calculated See table below

	Milligrams of Urine Urobilinogen	Milligram Daily Excreted in Feces
Obstructive Jaundice		
Uncomplicated stone	0-6	10-250
Stone with cholangitis or cirrhosis	4-50	10 250
Neoplasm	0-0.3	0-5
Hepatocellular Jaundice		
Cirrhosis	4 100	8 200
Hepatic disease with increased blood destruction	20- 00	300-1 00
Acute hepatitis	4 200	10-300
Hemolytic Jaundice		
Uncomplicated	1 10	300-1 800
Complicated by infection anemia crises infarction or anesthesia	10-300	300 2 500

Normal Values

Normal values are between 150 and 300 mg of urobilinogen per 100 gm of stool with extreme limits of 70 to 600 mg Any specimen of urine yielding a color in the range of the weak or intermediate standard may be regarded as not containing increased amounts of urobilinogen and should be reported as 'not increased' Colors in the range of the strong standard should be regarded with suspicion Values of over 8 mg per 100 c c of urine almost certainly represent pathological urobilinogenuria

BILIRUBINEMIA

Bilirubin accumulates in the blood as a result of excessive hemolysis or because of hepatic or biliary tract disease in which the liver is incapable of excreting the bilirubin produced in the normal break down of red cells Quantitative estimations of the amount of bilirubin present in the blood plasma and subsequent changes in the course of the disease are of prognostic value since rising concentration suggests increasing severity of the disease The degrees of bilirubinemia are usually expressed in terms of the icterus index or in actual milligrams of bilirubin per 100 c c of blood

In the icterus index method the color of the blood serum is compared with a standard solution of 1 10,000 potassium dichromate and the relative intensity expressed in units the normal values being 0 to 6 units Clinical icterus may not be detected until the icterus index has reached 15 Carotene which may cause some confusion in determining the icterus index does not affect the van den Burgh reaction Normal blood serum contains up to 0 8 mg of bilirubin per 100 c c

Test for Bilirubin in the Urine

Overlay 2 to 5 c c of urine with a 1 10 alcoholic dilution of tincture of iodine A green ring forming at the area of contact indicates bilirubin An observation equally informative but perhaps less scientific, is the tell tale stain on the patient s pajama pants

CEPHALIN CHOLESTEROL FLOCCULATION TEST

This test as introduced by Hanger is based upon the fact that in patients with active liver disease or damage the blood serum posseses the quality of flocculating a cephalin cholesterol emulsion whereas in the sera of normal subjects no flocculation occurs The density of flocculation varies directly with the degree of liver damage The test is simple and has particular merits in jaundice and in following the course of patients with liver damage Its value has been definitely established The cephalin cholesterol mixture is available commercially This appears to be our most sensitive liver function test

Interpretation A test reading of two plus, or over suggests liver damage

HIPPURIC ACID SYNTHESIS TEST

It is the belief of many clinicians that this test gives more information regarding the functional condition of the liver parenchyma than any other single test It can be employed in non jaundiced as well as in jaundiced patients and when it is repeated it is (possibly with the exception of the cephalin cholesterol test) the best index of the course of hepatic disease The test depends upon the ability of the liver to convert benzoic acid to hippuric acid which is subsequently excreted in the urine Both the oral and the intravenous test are used

Oral Method

One hour after a light breakfast of toast and coffee the subject ingests 6 grams of sodium benzoate dissolved in 30 c c of water and flavored with a little lemon juice or peppermint water This is followed by one half glass of water Immediately after taking the drug the patient voids and discards the specimen The urine is collected at hourly intervals *for the next four hours In the presence of* gastric retention or other conditions interfering with absorption from the gastrointestinal tract, the intravenous route may be used

Intravenous Method

One hour after a light breakfast 1 77 grams of sodium benzoate are given intravenously in 20 c c of distilled water The injection should be very slow and take at least 5 minutes or more to complete The patient should void before the test and exactly one hour after the dose has been given The one hour sample is sent to the laboratory If the specimen has to be sent through the mail toluene can be used as a preservative

Determination If the urine volume is more than 150 c c it should be made slightly acid with acetic acid and concentrated in a water bath The amount of precipitated hippuric acid can be determined either by titration or by direct weighing To the amount obtained must be added the amount remaining in solution It has been found that 100 c c of urine containing 50 grams of ammonium sulfate will dissolve approximately 0 1 gram of hippuric acid To express the hippuric acid in terms of benzoic acid the former is multiplied of 0 68 Healthy adults will excrete 1 0 to 1 4 grams of hippuric acid (equivalent to 0 7 to 0 95 gm of benzoic acid) Since 1 gram of hippuric acid can be accepted as the minimal normal output it is unnecessary to convert the weight of hippuric acid to benzoic acid in calculating the per cent of normal Normal individuals excrete an amount of hippuric acid equivalent to 3 grams of benzoic acid during the four hour period

This test has been found to be of great value in assessing the surgical risk of patients ith common duct stone and gall bladder isease White and collaborators have found that the postoperative course was favorable in those cases in which the hippuric acid excretion was between 2 5 and 3 6 grams before operation but when the excretion was between 1 0 and 1 5 grams the post-operative course was prolonged and unsatisfactory

Contraindications

The test cannot be performed in patients with renal disease or dehydration of a degree sufficient to interfere with the excretion of hippuric acid by the kidney It is wise to perform the urea clearance test simultaneously in order to exclude the possibility of renal impairment *The test is of little value in differential diagnosis* as it shows some degree of reduction in every type of liver disease

TAKATA ARA REACTION

This test is mentioned here solely to point out the fact that a plus reaction depends upon a reversal of the albumin globulin ratio This being true it is better to determine the albumin globulin ratio and get some exact figures which will be of diagnostic importance

ALBUMIN GLOBULIN RATIO

When the liver is diseased the total plasma protein is decreased and particularly the albumin fraction The albumin globulin ratio frequently approaches 1 1 Other conditions in which this ratio is disturbed must be excluded such as nephrosis severe alkalosis and occasional cases of hyperthyroidism When ascites is present the loss of albumin in the ascitic fluid or the increased capillary permeability allowing the escape of protein into the tissues may be a primary factor The production of albumin by the liver may be deficient and account for its low concentration in the plasma

GALACTOSE AND LEVULOSE TOLERANCE TESTS

In spite of the fact that many regard the galactose tolerance test as unreliable owing to the results being frequently equivocal it is widely used to differentiate between extrahepatic and intrahepatic jaundice The rationale of the test is based upon the fact that a normally functioning liver can utilize a dose of 40 grams of galactose without producing any change in the level of the blood sugar or su-

urine will produce only a weak pink color at the most The urine must be cooled to room temperature or lower before the test is run Quantitative determinations carried out on 24 hour specimens are best By comparing the color obtained with phenolsulfonthalein standards and applying the formula developed by Watson (Archives of Int Med 59 522 1937) the urobilinogen excretion per day can be carried out and calculated See table below

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3 Rise in the prothrombin time insufficiently relieved by vitamin K administration
4 Rise of the N P N
5 Drop in cholesterol esters
6 Rise in cephalin cholesterol flocculation test

Signs of Recovery

1 Rise of urinary urobilinogen in the face of a decrease in the bilirubinuria
2 Increased diuresis
3 Rise of the cholesterol esters
4 In beginning recovery from hepatitis the Graham Cole test may show a filling of the gall bladder
5 Drop in cephalin cholesterol flocculation test

LIVER FUNCTION TESTS OF VALUE IN NON JAUNDICED PATIENTS

Early Cirrhosis

1 Increased icterus index
2 Increased urobilinogen in the urine
3 Bromsulphalein retention
4 Low albumin fraction and reversed A/G ratio
5 Positive Cephalin Flocculation test—dense flocculation
6 Low cholesterol esters

Chronic Gallbladder Disease

Slight liver damage may be manifested in the presence of gallbladder disease by

1 Increased icterus index
2 Cephalin flocculation test—dense flocculation
3 Decreased hippuric acid excretion
4 Bromsulfalein retention

Before Starting Treatment or Restarting Treatment of Hepatotoxic Drugs

The following findings are suggestive of liver impairment

1 Increased urobilinogen in the urine
2 Bromsulfalein retention
3 Increased icterus index
4 Decreased hippuric acid excretion
5 Cephalin cholesterol flocculation test—dense flocculation

Hyperthyroidism

In hyperthyroidism impairment of liver function may parallel the degree of thyrotoxicosis The following may indicate liver damage

1 Galactose tolerance test—increased urinary excretion
2 Hippuric acid test
3 Cephalin flocculation test
4 Bromsulfalein test

Examinations of Blood

ANTICOAGULANT

An anticoagulant such as oxalate or citrate is used for sedimentation rate and hematocrit determinations

HEMATOCRIT

Blood for this determination should be drawn from a part in which there is no stasis Therefore, after the needle has been introduced into the vein, the tourniquet should be released and one full minute allowed to elapse before the blood is aspirated into the syringe After mixing the citrate the blood is placed in a Wintrobe hematocrit tube, and the tube is spun in the centrifuge at 3000 r p m for 30 minutes The calculation is

Reading on tube × 10 equals cells in per cent of whole blood

SEDIMENTATION RATE

This is recorded as the total fall of erythrocytes in one hour No correction is made for anemia The upper limit of normal for males is 10 mm for females 20 mm Three per cent sodium citrate is used as an anticoagulant

RETICULOCYTE COUNT

A 0 1 per cent brilliant cresyl blue in normal saline is used In a small test tube equal parts of blood and the dye solution (5 gtts each) are mixed A drop is spread on a glass slide or cover slip as for a differential count and when dry examined under oil

It is unnecessary to use Wright's stain Count 1000 red cells and record the percentage of reticulocyte This method gives significantly higher percentages than older methods

nificant glycosuria Recently the intravenous method has been used, this consists of injecting 100 c c of properly warmed sterilized and buffered solution of galactose Patients with normal livers show complete utilization of 25 grams of galactose within one hour Occasionally, the levulose tolerance test is used, normally the blood sugar is not affected by the oral administration of levulose, but it is increased in hepatic disease

BROMSULFALEIN TEST

Bromsulfalein is normally excreted by the liver through the bile In disturbances of biliary excretion, the blood level of the dye remains high after a test does has been injected The test is of no use in the presence of jaundice since both hepatitis and biliary obstruction interfere with its excretion A retention of the dye in more than traces is a sign of impaired biliary excretion and in the absence of jaundice of liver damage

Technique The patient is weighed and for each 22 pounds of weight, 1 c c of the sterile dye solution is drawn from the ampule and injected very slowly intravenously One hour later 5 c c of blood are withdrawn from the other arm, using a different clean dry sterile syringe The blood is placed in a dry test tube and sent to the laboratory with a request for a bromsulfalein determination

PHOSPHATASE TEST

Phosphatase which is normally present in the blood serum and bile may be increased in biliary obstruction either because of obstruction of the biliary flow or of regurgitation into the blood of phosphates in the bile

VITAMIN K THERAPEUTIC TEST

In the presence of a high prothrombin time a normal liver will respond to a therapeutic dose of synthetic vitamin K by a decrease of 10 to 15 per cent within from twenty four to seventy two hours In the presence of liver damage such a decrease will not occur

Other Tests

HISTAMINE TEST FOR JAUNDICE

In patients in whom the presence of jaundice is questionable the pigmentation can be accentuated by raising a histamine wheal Inject 0 05 c c of a 1 1000 histamine hydrochloride solution intradermally The anterior surface of the chest is a good site In the formation of the wheal, plasma proteins escape from the capillaries into the skin carrying bile pigments with them The area of the wheal therefore takes on a more yellow tint than the surrounding skin This will not differentiate carotenemia

TEST FOR CAROTENEMIA

Add 2 0 c c of blood serum to 8 c c of 95 per cent ethyl alcohol Add 2 0 c c (low boiling point) petroleum ether Shake vigorously When the emulsion separates, yellow carotene pigment colors the upper layer while bile pigment remains in the lower alcohol layer For comparison it is well to do a control test on a normal serum or the serum of a patient with icterus

CRITERIA POINTING TO IMMEDIATE SURGERY IN OBSTRUCTIVE JAUNDICE

1 The sudden rise of the icteric index from a fairly constant level points to a secondary parenchymatous complication

2 If in a jaundiced patient under observation either the prothrombin time rises or worse, if a hemorrhagic diathesis appears, severe secondary liver damage has developed This is confirmed by an inadequate response to further vitamin K therapy

3 A sudden rise of the non protein nitrogen in a patient with jaundice is a danger sign

4 Increased alimentary galactosuria or decreased excretion of hippuric acid

If upon the repetition of these tests the previously normal results have become abnormal the development of a secondary hepatitis is indicated

5 In severe liver damage increased amounts of amino acids may be present in the blood and thus tyrosine appears in the urine This is detected by Millon s test

PROGNOSTIC SIGNS IN ACUTE HEPATITIS (4)

Signs of Liver Failure

1 Rise of the icterus index
2 Millon s test becomes positive

3 Rise in the prothrombin time insufficiently relieved by vitamin K administration
4 Rise of the N P N
5 Drop in cholesterol esters
6 Rise in cephalin cholesterol flocculation test

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It is unnecessary to use Wright's stain Count 1000 red cells and record the percentage of reticulocytes This method gives significantly higher percentages than older methods

PLATELET COUNT

Blood is drawn directly from the finger tip into a standard red cell counting pipette to the 0.5 mark and diluted 200 times by the addition of 3 per cent sodium citrate solution (freshly prepared or freshly filtered). The diluted blood after shaking is then placed in a standard counting chamber, and the platelets within the square millimeter are counted, the final figure being multiplied by 2000, thus giving the number of platelets per cubic millimeter of blood. The normal number of platelets by this method is 150 000 to 350 000 per cubic millimeter. 100 000 platelets or below is abnormal.

USE OF THICK FILMS IN THE DIAGNOSIS OF MALARIA

See section of Malaria, page 802.

HEMOGLOBIN

Sahli Test. A small puncture is made in the lobe of the ear and blood drawn into the special Sahli pipette up to the 20 cmm. mark; the tip of the pipette is wiped and the blood expelled immediately into the special graduated Sahli test tube, in which there has been placed 0.1/N HCl up to the 10 cmm. mark. The blood should be expelled with the tip of the pipette beneath the acid level. The pipette is then rinsed with the acid several times in order to wash out the last traces of blood. Care should be taken to expel every trace into the test tube and not to allow drops on the outside of the pipette to be lost. The test tube is placed in the comparison colorimeter and distilled water added drop by drop, stirring with a glass rod after each addition, until the depth of the brown color matches that of the permanent standard. The hemoglobin may be read off from the test tube either in grams per 100 c.c. or in percentage. The reading corresponds to the level of the diluted acidified blood.

LEUCOCYTE COUNT

A solution of 2 or 3 per cent acetic acid is prepared and a few drops of 5 per cent copper sulphate added to prevent the growth of yeasts. A small puncture wound is made in the lobe of the ear or tip of the finger and blood drawn into a white cell pipette to the 0.5 mark. The tip is wiped and acetic acid drawn up to the 11 mark. The pipette is shaken well and a few drops expelled to fill the counting chamber. With the low power objective and reduced illumination, the cells in 4 of the large corner squares (1 mm. x 1 mm.) are counted and the result multiplied by 50.

When high counts are expected, as in leukemia, it is more satisfactory to use a red cell pipette, drawing the blood up to the 1 mark and diluting with acetic acid to the 101 mark. A count is made as before, but the result is multiplied by 500 instead of by 50.

ERYTHROCYTE COUNT

Either Hayem's or Gowers' solution may be used. The solution should be freshly filtered. Draw blood from a fresh puncture wound into a red cell pipette up to the 0.5 mark. The tip is wiped and the diluting fluid drawn up to the 101 mark. The pipette is shaken well and a few drops expelled to fill the counting chamber. With the high dry objective and with decreased illumination a count is made as follows:

1. In the old style ruling there are 25 small squares (each $\frac{1}{400}$ mm. square) enclosed in a large square of doubly ruled lines. The cells are counted in 4 such squares (100 of the smallest squares) and the result multiplied by 8000.
2. In the new style ruling there are 16 small squares (each $\frac{1}{400}$ mm. square) enclosed in a large square of doubly ruled lines. Count the cells in 5 such squares (80 of the smallest squares) and multiply the result by 10 000.

Sources of Error

If Hayem's solution causes agglutination of the red cells, Gowers' solution must be used instead. When agglutination occurs, it is strong evidence of a high serum protein and calls for a serum protein determination and a careful search for Bence Jones protein in the urine. With high erythrocyte counts it is advisable to draw the blood up to the 0.2 mark and to multiply the final result by 2.5.

STAINED SMEARS

Glass cover slips (preferably [illegible]/8 inch) should be cleaned by immersion for some time in con

centrated nitric acid After removal from the acid they are placed edges down in a large glass funnel The latter is stood in a ring stand in a sink and one end of a piece of rubber tubing attached to its stem, and the other end to a water faucet Water is allowed to flow upward through the funnel at such a rate that the cover slips are continuously agitated a screen being laid over the top of the funnel to prevent their escape After one half hour of washing they are drained and immersed in 95 per cent alcohol They are then dried each separately with a piece of *clean* gauze

A fresh puncture is made in the lobe of the ear and only a small drop of blood allowed to well up (about 2 mm in diameter) This is picked up on a cover slip and another cover slip immediately dropped upon it The blood is allowed to run to the edges and the cover slips are then pulled quickly apart keeping them parallel With a little practice with this method smooth thin smears may be obtained on which the leucocytes and platelets are fairly evenly distributed

The smears should be allowed to dry face up When dry one of the thinner smears should be covered with from 3 to 5 drops of Wright s stain and allowed to stand one minute then 6 to 8 drops of buffer solution are added The slip is tipped back and forth to give complete mixing It is allowed to stand three minutes then flooded gently with water until the stain is washed off blotted dry and mounted on a glass slide with balsa

With the oil immersion objective a differential count of 100 leucocytes is made (In special cases it may be desirable to count 200 cells)

a Polymorphonuclears
b Lymphocytes
c Monocytes
d Eosinophiles
e Basophiles

One should determine whether the platelets are increased normal reduced or absent Normally in a well made smear there are from 20 to 50 platelets for every leucocyte when the white cell count is normal Describe the red cells noting anisocytosis poikilocytosis macrocytes microcytes polychromatophilia stippling Howell Jolly or Cabot ring bodies achromia and intracellular or extracellular parasites

In abnormal bloods include the following in the differential count

Young polymorphonuclears (stab forms)
Myelocytes
Eosinophilic or basophilic myelocytes
Myeloblasts
Normoblasts
Megaloblasts
Megakaryocytes

Lymphoblasts and any unclassified or atypical cells should be described carefully

Sources of Error

Poor staining is usually due to faulty technique Use only a certified stain and buffer solution Dilute the stain with buffer solution rather than with water By doing so a better stain is secured the malarial parasites red blood cells and hemoglobin are better seen The amounts of buffer solution and stain to be used can only be learned from experience In humid weather light staining may be improved by warming the smear gently before adding the stain

CELL VOLUME AND HEMATOCRIT

Sufficient anticoagulant solution should be placed in a test tube and boiled over an open flame until all the water and vapor have been driven off leaving the salt in the dry form With a clean dry syringe and needle, exactly 5 c c of blood should be drawn from the arm vein and transferred quickly to the prepared test tube and mixed at once to prevent clotting

The Test

The test tube is agitated for several minutes to insure an even distribution of cells and plasma

1 Blood is drawn into a certified red cell pipette, diluted with Gowers or Hayem s solution and an accurate count made of the venous red blood cells (See erythrocyte count)

2 The test tube is again agitated and with a medicine dropper drawn out to length of 10 cm and of capillary caliber a little over 1 c c of blood is taken up and immediately transferred to a Wintrobe sedimentation rate tube, filling the latter accurately to the 0 mark The tube is then placed in the centrifuge counter balanced and spun at 2,00 r p m for 30 min

utes It is then removed and the per cent of cells recorded (Hematocrit reading)

The average cell volume in cubic micra is given by the following formula

$$\frac{\text{Per cent volume of cells} \times 10}{\text{Venous red blood cells in millions}} = \text{the cell volume}$$

The normal is 80–95 cubic micra

Sources of Error

Insufficiently mixed samples give erroneous figures Too much or too little sodium oxalate, or insufficient drying of the tube produces large errors A centrifuge which revolves less than 1500 r p m gives higher figures unless it is run for a longer length of time When properly carried out, this test gives extremely important information in regard to the question of megalocytic anemia and should not be attempted without adequate preliminary personal instruction

BLEEDING TIME

With a Glover's needle a deep puncture is made in the lobe of the ear It should not be squeezed At intervals of thirty seconds the accumulated blood is blotted gently with filter paper This is repeated until no further free oozing is observed The bleeding time is calculated from the time of the puncture until the cessation of bleeding The test at best is subject to considerable variation For practical purposes a bleeding time which is repeatedly longer than five or six minutes may be considered abnormal

COAGULATION TIME

Apparatus

Five small test tubes (0 8 x 7 cm) are cleaned with dichromate sulphuric acid cleaning fluid rinsed thoroughly with distilled water and dried in an oven or incubator The five tubes are placed in a rack

Technique

Obtain by venous puncture 8 c c of blood with as little trauma as possible After the needle has been removed, transfer 1 5 c c of blood carefully to each test tube Calculate the clotting time from the time of puncture After two minutes tilt the first tube and very minute thereafter until that tube can be inverted without disturbing the blood Agitate the tube gently in order to be certain that clotting is complete Rough agitation may cause defibrination and should therefore be avoided Surface coagulation may appear within the normal time of from six to ten minutes, but it may take much longer for a firm clot to form throughout After the first tube has firmly clotted, examine the second If the clot is not quite firm, tilting should be done as with the first tube If the clot in the third tube is not firm, repeat the process The clotting end point is the moment when one of the tubes, occasionally the third, but usually the fourth or fifth, is found to contain a firm clot when it is inverted for the first time

Record the clotting time of each of the five tubes Place them in the incubator for twenty four hours to observe the clot retraction

Sources of Error

The errors are chiefly on the side of shortening the clotting time, and these may be due to either an unclean syringe, needle or tubes trauma to the tissues about the vein or to aspiration of air through the blood into the syringe, producing a foam The presence of oxalate, citrate etc , in the syringe or tube will prolong the clotting time

CLOT RETRACTION

Place the tubes described above in an incubator at 37 5°C and observe after twelve to twenty four hours Normally definite retraction may be observed in six hours but the process is often not complete before eighteen hours The color and firmness of the clot should also be noted

Source of Error

No clot retraction will occur if the blood has been considerably agitated while clotting

THE ESTIMATION OF THE RED CELL FRAGILITY

Principle

The toughness of the red cell membrane is tested by immersion in varying strengths of hypotonic sodium chloride solutions

Reading the Reaction After an hour or when the cells settle note

a The dilution at which hemolysis begins as indicated by a very slight yellow coloring of the supernatant fluid just above the cells with a moderate deposit of cells at the bottom of the tube Normal 0 45 per cent

b The dilution at which hemolysis is complete is indicated by a deep red color of the supernatant fluid with an absence of any cell deposit at the bottom of the tube Normal 0.35 per cent If tests are done infrequently a control test of cell fragility should be made on normal blood

Interpretation The terms 'increased red cell fragility to hemolysis' and decreased resistance or tonicity to saline have the same significance In congenital familial hemolytic icterus and occasionally in the acquired type the cells show increased fragility Persons with these diseases on account of the marked hemolysis of their blood during hemolytic crises frequently develop gall stones After the spleen has been removed attacks of jaundice do not recur although the red cell fragility remains unchanged Patients suffering from obstructive jaundice due to hepatitis, gall stones or malignancy show decreased fragility that is their red cells have more than the normal resistance to saline In pernicious splenic and certain secondary anemias and especially in the type due to gastrointestinal cancer the red cell fragility is also reduced A notable exception is the anemia that occurs with dysphagia in Plummer s syndrome the red cell fragility being increased

Examination and Collection of Specimens—*Routine Studies*

URINE

The urine should preferably be fresh When examining for pathological elements a specimen passed three hours post cibum should be examined since early morning specimens are the least likely to contain pathological elements It may be necessary to examine repeated samples taken during the day when looking for cyclic albuminuria

Urine decomposes at warm temperatures Preservatives are on the whole unsatisfactory but the following are used (a) Thymol—a small lump added to the urine will preserve it for several days but it may cause a false positive albumin reaction (b) Formalin is used 1 drop per ounce of urine This interferes with the test for indican (c) Toluol is the best preservative

Color of the Urine	Cause
Colo les	M y be d e to e es e dil tion d betes gran l r kidney evere a m s oth than P anemia
Milky	Chyl a o a purul t disch ge from th G U t t
R d	Hem rrhage phe olpht l n he m globinu ia m c och ome pyrid um
O ge	Santonin rysopha c acid pyrid ium
G ee Yellow to B own or Black	J dice (will f am wh n shaken)
Dirty Gree Blue	S en in p t efying urine typhus ch l or when m thylen bl e h be n t k
B wn Yell w or B wn Red (acid) B ight Red (alkaline)	These m y be due t senna rb barb cara o argyrol
Dark B own B own Red o Y llow	Seen in a te f bril disease

Record

1 Hour passed
2 Color
3 Clearness or turbidity
4 Reaction—blue litmus should be used acid renders it red alkali blue If the test is alkaline the litmus should be dried with heat if the blue color disappears, it was due to ammonia In alkaline urine passed after meals remember the physiological alkaline tide
5 *Specific gravity* The urinometer should float freely A correction should be made if at body temperatures 0 001 to the S G for each 3 C above the temperature for which the urinometer is standardized 0 001 is subtracted for each 3°C below the standard

Laboratory Tests of Value

Albumin *Heat Test* Almost fill a test tube with urine and heat the upper portion of the tube for two minutes If a cloud forms and fades away with the addition of several drops of 5 per cent acetic acid it was due to phosphates or carbonates Faint traces of albumin may be indicated only after the addition of the acid

Record the findings

— No cloudiness
+— Faint trace

+ Trace but no granularity or flocculation
++ Granular cloudiness but no flocculation Seen from above the cloud is dense but not opaque It is about 0 1 per cent protein
+++ Dense opaque cloud clearly flocculated It is about 0 2 to 0 3 per cent protein
++++ Very heavy precipitate It is about 0 5 per cent or more protein

Robert's Ring Test Place a few c c of Robert's reagent in a conical glass or test tube Tilt and run clear urine from a pipette or medicine dropper down the side to give a sharp line of contact If albumin is present, a white ring appears at the line of contact It is best seen against a black background at a distance of several feet This test is more satisfactory than the Heller Ring test which employs nitric acid as it is sensitive and does not form other confusing rings due to indican and bile pigments At times a secondary ring may confuse due to uric acid and urates This ring is broader and is usually above the albumin ring

Sugar To 5 c c of Benedict s solution (about 1 inch in a test tube of ¾ inch diameter) add 0 25 c c (5 drops not more) of urine Heat over a flame for one to two minutes shaking the tube to prevent the solution spurting out or better stand the tube in a boiling water bath for 5 minutes not more

Negative Clear blue color or bluish green with a gray precipitate

Positive Opaque with a yellow or red sediment The amount of sediment depends upon the percentage of sugar present If the result is doubtful allow to cool spontaneously before reading If the sugar test is positive test for ketone bodies by the nitroprusside test

Quantitative Sugar Determination Dilute 10 c c of urine with 90 c c of water and set aside in a flask Add 10 grams of crystalline sodium carbonate to 25 c c of Benedict s Quantitative solution in a flask Add a few glass beads or a pinch of powdered talc to the reagent Heat is then applied to the reagent until boiling at which time the urine mixed in the flask is run in a little at a time drop by drop from a graduated pipette until the blue color disappears Record the amount of diluted urine used The reagent is so prepared that 25 c c are reduced by 0 05 gram of glucose The number of c c of diluted urine used therefore contains this amount

Calculation Divide the amount of diluted urine by 10 which gives the amount of undiluted urine carrying 0 05 gram of glucose Divide 0 05 by the number of c c of undiluted urine to obtain the amount of sugar contained in 1 c c of urine This figure is then multiplied by 100 to obtain the percentage, or by the total number of c c in the 24 hour specimen to obtain the number of grams voided

Diacetic Acid *Gerhardt's Test* To 5 c c of urine add a slight excess of 10 per cent ferric chloride solution drop by drop until the phosphates are precipitated Filter To the filtrate add more of the ferric chloride solution If diacetic acid is present the solution will turn a Bordeaux wine red color Since a similar color will result from the presence of phenol salicylates antipyrine sodium bicarbonate or other substances it is necessary to repeat the test as follows

1 To 5 c c of urine add 5 c c of water and boil down to 5 c c or one half its original volume After cooling add the ferric chloride as before Since boiling drives off the diacetic acid if the color develops, its presence is due to other substances

Bile

1 Shake vigorously a test tube half filled with urine and note the color of the foam A yellow color is ordinarily regarded as evidence of the presence of bile Sources of error are the fact that lemon color cannot be seen under artificial light Urates at times may give a reddish hue
2 A simple test is that of overlying urine in a test tube with tincture of iodine A green color at the junction of the two liquids denotes the presence of bile

Microscopic Examination

A well mixed drop of sediment is examined under a cover glass using the low power lens with subdued light One should look for

a Pus cells
b Red blood cells
c Casts

Cells If more than 50 cells are found under the low power field there will be over 3 per high power field Pus cells should be differentiated from red blood cells under the high power lens the approximate number per high power field being recorded after examining 10 microscopic fields and any clumping of the pus cells noted Over 100 cells should be recorded as ' much pus or much blood

Casts The low power lens should be used and if more than 3 typical casts are found the approximate number seen in the whole sediment should be stated over 100 being reported vesical outlet, so bladder and upper portion of the urinary tract is clear

Pus in Both Sediments Source is from the bladder or above or from a pus pocket from or between the vesical outlet and the anterior extremity of the bulbar portion of the urethra More study is necessary

Triple Phosphates Present This suggests urinary stagnation and if the bladder has been really emptied kidney pelvis stagnation is likely and x ray studies should be made

Squamous Epithelium in 2nd Specimen There is no doubt that cystitis is present The

First Glass	Second Glass	Possible Urinary Picture
Cloudy	Clear	Anterior urethritis (acute) Same with mild or subsiding posterior involvement
Hazy	Clear	Mild acute or subacute anterior urethritis Same with mild posterior involvement Epithelial desquamation from overtreatment or stricture
Shreds	Clear	Subsiding anterior urethritis Subsiding anteroposterior urethritis Chronic urethritis generally as the result of deeper foci of infection in the prostate or other associated small channel
Cloudy	Cloudy	Acute anteroposterior urethritis Cystitis or upper tract suppuration Subacute or mild anteroposterior urethritis
Hazy	Hazy	Same as above Bacteriuria
Clear	Cloudy	Seminal fluid Contents of pus pocket Sedimented mucus or phosphates from a poorly emptying bladder Slight terminal bleeding

From Pelouze Office Urology W B Saunders Co Philadelphia 1940 p 83

as numerous They do not have the tapering ends or tails as have cylindroids When more than half the cast is clear it is reported as hyaline when more than half is granular it is termed regular Pus casts blood casts or epithelial casts are reported as such The high power lens may be necessary to distinguish the cells or casts

Two Glass Study of the Urine The patient voids into two glasses With a pipette a small amount of sediment from each specimen after centrifuging is placed on slides overlaid with cover slips and examined under reduced illumination

Pus in the First Glass Source is distal to cause should be sought since the condition is chronic

Motile Bacilli in Otherwise Negative Urine A colonic source of bacteria should be sought

Large Clumps of Cocci with or without Pus The emptying possibilities of the kidney pelves should be investigated or a displaced kidney with a dilated pelvis and ureter excluded The stained specimen should be examined

Clear Urine Shows Calcium Oxalate Crystals One should look for red blood cells and x ray for calculi If not found repeat in three months Determine whether the patient has been eating grapefruit rhubarb

+ Trace but no granularity or flocculation
++ Granular cloudiness but no flocculation Seen from above the cloud is dense but not opaque It is about 0 1 per cent protein
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b Red blood cells
c Casts

logical significance Their dumb-bell shape resembles that of crystals of calcium oxalate but they are quickly soluble in dilute acetic acid

Calcium Phosphate The presence of these may suggest urinary stagnation They are true evidence of alkalinization and are often seen in gonorrheal urine Their solubility in acetic acid differentiates them from sodium urate crystals

Calcium Oxalate This is the only crystal which in itself may produce symptoms causing burning and frequency of micturition The crystals are not dissolved by acetic acid They are common in those eating large amounts of tomatoes rhubarb grapefruit spinach, apples or carbohydrates They may appear in diabetes mellitus constipation organic liver disease and in disease of the heart and lungs with anoxia

Uric Acid As a rule these occur in gout interstitial nephritis, fevers those on a high protein diet

Urates The ammonium urate crystal suggests urinary stasis if found in freshly voided urine

Leucin and Tyrosine These are not often found but are always found together They are present in Acute phosphorus poisoning acute yellow atrophy of liver, cirrhosis of liver typhoid fever (severe)

Study of Urine Sediment It will facilitate the study of the urinary sediment if the cells are washed with distilled water or saline This procedure enlarges the cells A test tube of urine is centrifuged and inverted quickly to pour off the supernatant urine Distilled water or normal saline is then poured into the tube which is shaken to mix the sediment thoroughly The tube is again centrifuged and inverted and the supernatant fluid poured off The tube is kept inverted and the material for a spread is obtained from the tube tip and spread on a slide dried and fixed by gentle heat Stain by the Gram method

Prostatic Secretion This should be washed in the same manner as mentioned for urinary sediment If this is not done it may peel off the slide The secretion is allowed to fall into a tube containing saline or distilled water The tube is shaken until a homogeneous suspension is formed and the mixture than centrifuged and treated as for urinary sediment

Semen The same method as for prostatic secretion is advised

Shreds Allow these to form a sediment and then wash as advised for urine specimen The specimen should be shaken well to break up the shreds

Examination of Urine for Tubercle Bacilli A catheterized specimen is not necessary In the male the second specimen can be used The female can wash the vulva and spread the labia apart as she urinates The first portion should be then discarded and the second portion used for study

Take the specific gravity reading If it is high, place the urine in a tall beaker and add an equal amount of distilled water After sedimentation pour off the supernatant fluid If there is a large amount of pus the following methods are recommended

1 The specimen is placed in a centrifuge tube and after shaking well centrifuged at low speed to throw down the heavy elements but not the bacteria The supernatant fluid is poured off and the specimen centrifuged at high speed and washed as previously described The specimen is then recentrifuged and a portion taken from the tip of the inverted tube Part of the sediment can be injected into a guinea pig if the test is positive the pig will show signs within 6 weeks
2 If it is a 24 hour specimen this method is of value If it contains phosphates it may be necessary to remove them by acidification An equal amount of antiformin should be added and mixed with the sediment which is allowed to stand in an incubator for half an hour Distilled water is used to reduce the specific gravity before final centrifugation

STAINING METHODS OF SMEARS

Modified Gram Stain

1 Crystal violet for 5 seconds then flood with soda bicarbonate solution
2 Flood with iodine solution pour off and reflood allowing it to act about 5 seconds (This is the most important step if washed off too quickly there will be a great increase in the amount of gram negative elements of the normally gram

tomatoes, apples, carbohydrates in large amounts or is constipated

Blood in 1st or 2nd Glass One should not believe that all terminal bleeding is due to an abnormality at the vesical outlet While this is usually true, it also occurs in carcinoma, vesical papilloma, or stone A cystoscopic study is indicated

Blood in Both Glasses Cystoscopy is imperative and is best done while the bleeding is active

Yeast Cells in First Glass Sugar should be looked for, if none found one should suspect the reagent

If the addition of dilute acetic acid increases cloudiness, it will be because the patient is probably taking one of the balsamic drugs

Reaction of Urine Normal fresh voided urine should show a reaction on the acid side of neutrality High protein diets increase the acidity while vegetable diets decrease it High nervous states are said to reduce the acidity of the urine In infections with staphylococci Salmonella or micrococci the reaction will tend to the alkaline side Colon or tubercle bacilli infection tends to cause acidity

Albumin in the Urine If the sample is not clear it can be made so by filtration or centrifugation When bacteruria renders its examination difficult the urine can be clarified by adding a teaspoonful of purified talc infusorial earth, or animal charcoal to each 2 or 3 ounces of urine shaking well and filtering through two thicknesses of filter paper

Pus Cells in the Urine It is not always a simple matter to differentiate pus cells from small round epithelial cells of the upper urinary tract or deeper layers of the lower urinary tract The following suggestions may be of help

1 One drop of dilute acetic acid under the cover slip will accentuate the nuclei
2 If any doubt still exists allow one drop of Gram s iodine to flow under the cover slip This stains the pus cells more deeply than the epithelial cells and accentuates the nuclei of both
3 It is well to remember that in acid urines the pus cells are much smaller than in alkaline urines In alkaline urines the cells are swollen, lack granules and the nuclei are scarcely seen
4 If the urine is of high specific gravity and one is in doubt about the cells it is well to centrifuge the urine, pour off the supernatant fluid, shake the sediment in some distilled water and recentrifuge the mixture The sediment can then be stained

Significance of Epithelial Cells in the Urine The external parts should always be well cleansed to avoid epithelial cells getting into the urine If this precaution has been observed, a fairly large quantity of epithelial cells in the urine can be considered significant

	Probable Site of Origin
Large amounts in 1st glass few in 2d	Urethral origin
Large amounts in both glasses	Upper tract and urethra
Many small round cells with epithelial casts	Renal tubules
Spindle shaped cells	Seminal tract
Large coarsely granular cells	*Prostate gland*
Large amount of squamous cells	Vesical irritation in females
Many squamous cells in 1st glass	Urethral trauma or stricture

Blood in the Urine A simple test is the benzidine test using tablets which can be purchased from E R Squibb and Co A very delicate test is the Stone Burke test, the procedure and technique of which follows

Solution No 1	
Orthotolidine	0 5 gm
Methyl alcohol	50 0 c c
Solution No 2	
Glacial acetic acid	15 0 c c
Hydrogen peroxide	50 0 c c

Procedure To 2 c c of urine add 2 drops of solution No 1 and mix thoroughly by shaking Then add three drops of solution No 2

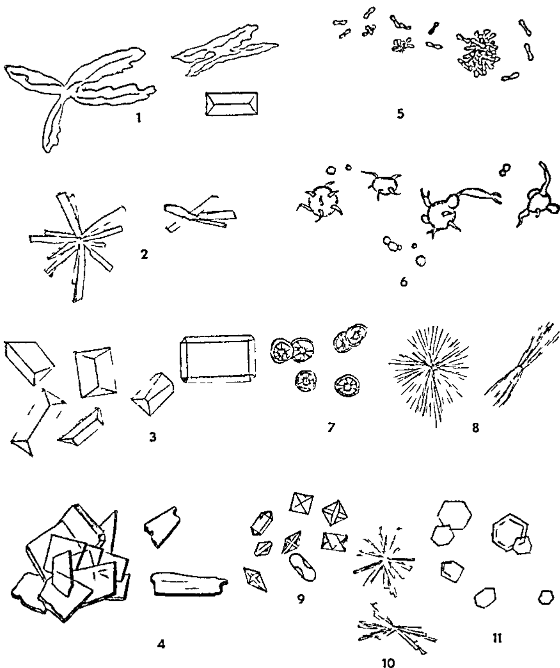
Interpretation

1 A greenish blue color appearing in the sediment of the centrifuged urine and persisting for one minute, denotes the presence of approximately 1 300 to 1 500 red blood cells per c c of urine
2 A deeper blue color persisting for one minute indicates 1 000 to 7 000 red blood cells per c c of urine
3 A deep blue persisting two minutes or longer indicates 15 000 to 20 000 red blood cells per c c of urine

Crystals in Urine

Triple Phosphates If the urine sample is fresh this signifies urinary stasis

Calcium Carbonate These have no patho



Nos 1 and 3 Triple phosphate crystal
No 2 Calcium phosphate crystals
No 4 Uric acid crystals
No 5 Calcium carbonate crystals
No 6 Ammonium urate crystals
No 7 Leucine spheres
No 8 Tyrosine needles
No 9 Calcium oxalate crystal
No 10 Sodium urate crystals
No 11 Cystine crystals

PLATE XI
Microscopic Examination of the Urine

positive cocci and they may be mistaken for gonococci)

3 Wash slide with acetone until no more color comes away (5 seconds)
4 Wash with distilled water—1 second
5 Apply basic fuchsin solution for 2 seconds
6 Wash again with distilled water and pass slide carefully through flame with the spread uppermost, to dry for study

Gram Stain Reactions of Bacteria Common to the G-U Tract

Gram Negative Gonococcus, coli group *Micrococcus catarrhalis* Ducrey bacillus, typhoid group *B pyocaneus*

Gram Positive Staphylococcus streptococcus pneumococcus Doderlein bacillus diphtheria bacillus diphtheroids

Stain for Tubercle Bacilli

1 Place slide where it can be kept just slightly steaming for about 5 minutes after flooding it with Ziehl Neelsen solution
2 Wash off the stain
3 Wash with acid alcohol until no more color comes away
4 Wash with water
5 Counterstain for 30 seconds with methylene tube

Microscopic Interpretation of Smears of Urethral Discharges

Not all urethral discharges are caused by the gonococcus nor is the urethra necessarily affected alone About 30 per cent of urethral discharges are non gonococcal The normal urethra commonly harbors the staphylococcus streptococcus diphtheroids and the pneumococcus, finding that one of these predominates does not justify the conclusion that it is the cau e of the discharge

I the Presen e of	Su pect
Prof se p rule t di ch rge cont ng no b cter	Ch m c l rr t nt j ct d to the rethra If t ntinu e amin a f sh pe imen for t i hom ad pa ti ul ly the prostat e t
Dis-ha g from u th a dis pl yi g any induration or ulce t n at or near the m t s	Th tr po m ot th t nd ng m ny b te s n n the st n d sm r A d rk fi ld study h ld b m de
La g n mb r of d phther d	P ol nged hem l t um
Many varied kinds of bacteria	Chem cal or instrumental trauma unclean preputial s c or i ritating vaginal se cret ons
Many intrac llular staphylococci or streptococci	An underlying focus in the p o-state gland

Interpretation of Prostatic Smear

1 Studies should be repeated 2 or 3 days apart
2 If pus is present on the 2nd or 3rd massage, there is a deep seated infection
3 If the lecithin granules completely fill the field the gland carries a deep infection A massage within four or five days will confirm this suspicion
4 More than 5 leucocytes per high power field suggest further study
5 Poor drainage should be suspected if clumps or leucocytes are found If the gland is massaged twice weekly for from 4 to 6 weeks, the clumps should disappear but a few leucocytes may persist If the condition continues disease of the posterior urethra should be suspected
6 The teeth and tonsils should be examined for foci of infection If these exist the prostate can rarely be freed of pus cells
7 Large numbers of red blood cells in the smear suggest that the massage has been too vigorous when they are found, one should stroke only the lateral lobes lightly

Interpretation of the Seminal Fluid Smear

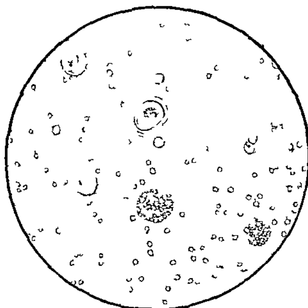
In order to reduce the amount of prostatic fluid in the specimen carefully strip the prostate gland and have the patient pass some urine In the presence of prostatic infection one will find varying numbers of pus cells in the more fluid areas of the smear and no positive means of knowing whether they have come from the seminal vesicles If on focusing up and down pus cells are found at various levels it can be assumed that an infected seminal vesicle exists Diagnostic methods are uncertain at best Condom specimens are no more reliable

EXAMINATION OF SPUTUM

Gross Examination

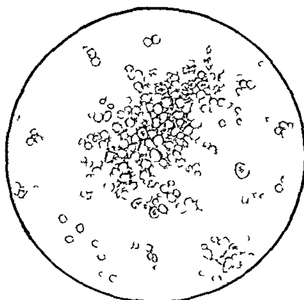
Record

1 Amount—estimate in ounces or cubic centimeters



(From Pelouze Office Urology W B Saunders Co)

FIG 229 The microscopic appearance of normal prostatic secretion The laminated bodies are corpora amylacea The other large cells are prostate granule cell The next smaller are polymorphonuclear leukocytes in normal numbers The remainder of the field is studded with lecithin bodies which are characteristic of this secretion



(From Pelouze Office Urology W B Saunders Co)

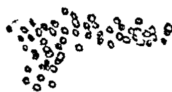
FIG 230 Prostatic secretion of a poorly draining infected gland The scarcity of lecithin bodies in such secretions is very striking As the leukocytes decrease in number the e increa e

2 Color—white yellow, green rusty, bloody
3 Odor—odorless foul musty
4 Consistency—thin mucoid tenacious thick pus
5 Tendency to separate into layers

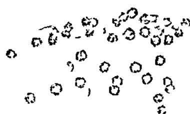
Gram Stain (Modified)

Solutions required

1 1 per cent aqueous solution of methyl violet 6 B



12



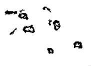
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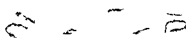
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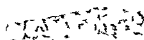
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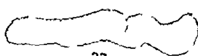
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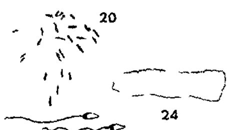
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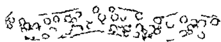


22



23

24



25

No 12 Blood cast
No 13 Pus cells (Leukocytes)
No 14 Epithelial cell cast
No 15 16 17 Epithelial cells
No 18 Mucus threads
No 19 Cylindroid

No *20* Bacterial cast
No *21* Granular cast
No 22 Hyalin cast
No 23 Spermatozoa
No 24 Waxy cast
No 25 Blood cast

PLATE XI *(continued)*
Microscopic Examination of the Urine

In making up the stain use only the purest chemicals

Antiformin Method for Tubercle Bacilli Solution Required

Solution chlorinated soda 5 per cent (filter)
Solution caustic soda 15 per cent (filter)
Take equal parts and mix well

Technique A measured quantity of sputum is placed in a clean flask and mixed with an equal quantity of 50 per cent antiformin the mixture is boiled gently over a Bunsen flame for fifteen minutes and then allowed to cool To each 10 c c of the fluid 1 5 c c of a mixture of chloroform (1 part) and alcohol (9 parts) are added The flask is shaken vigorously until a fine emulsion is produced A clean centrifuge tube is filled with the emulsion and centrifuged at high speed for twenty minutes The supernatant fluid is decanted and a portion of the film which has collected just above the chloroform layer is transferred to a clean cover slip A small amount of egg albumin or of the original sputum is added, mixed spread in a thin smear dried fixed with heat and stained for tubercle bacilli

Pneumococcus Typing (Neufeld)

A loopful of sputum from the blood flecked or cheesy portions of the specimen is picked out and placed on a clean glass slide With a fine capillary pipette 1 drop of Loeffler s methylene blue and 2 loopfuls of rabbit serum for pneumococcus typing (Lederle Squibb or Parke Davis) are added mixed together quickly and covered with a cover slip the latter being pressed down firmly The slide is allowed to stand at least ten minutes before reading Examination is made under oil immersion

When pneumococcus like organisms are found any swollen capsules should be noted If only organisms with normal capsules are seen the slide should stand another ten minutes and the hunt continued If pneumococci with swollen capsules are found their relative number and the type serum used in the test should be reported

Note The sets of rabbit sera for typing (Lederle Squibb or Parke Davis) contain 32 separate vials for 32 types of pneumococci These vials also contain methylene blue therefore no dye should be added unless the serum seems too pale in color

The sputum should first be tested with the sera mixtures (A B, C D E and F) until one is found to give a positive reaction By reference to the directions accompanying the set, one should determine which specific type sera are contained in the particular mixture used In a similar manner typing should again be done with each of the sera comprising the mixture and the type found reported It saves time to type with all the mixture simultaneously and also to type out with all of the specific sera comprising the mixture showing a positive test

Cultures After examination of the stained smear cultures should be made on a blood agar plate for *Streptococcus hemolyticus Staphylococcus aureus*, *B pneumonia* or *B influenza*

Methods of Examination of the Gastric Contents

GASTRIC ANALYSIS

1 The tube is passed and all fasting contents removed The patient should have fasted for at least 12 hours previously
2 A test meal of 50 c c of 7 per cent alcohol is given through the tube
3 After 20 minutes all of the contents are withdrawn and a test made for the presence of free HCl with congo red paper
4 If free HCl is present, there is no need to give histamine, inasmuch as unpleasant reactions occur in some patients
5 If no free HCl is present, histamine 0 005 mg per kilo of body weight is injected subcutaneously, and after 20 minutes the third specimen is withdrawn
6 Labelled samples should be sent promptly to the laboratory where they will be titrated for free and combined acid Occult blood *means nothing* as there is usually some trauma
7 *Properties of Stomach Contents*
   Amount—50 to 100 c c normal fasting contents Increase may be due to hypersecretion, retention or regurgitation from the duodenum
   Color—Colorless or green normally yellow from bile regurgitation from the duodenum when not due to retching the increased bile may be due to intestinal obstruction or ileal stasis Red brown, or black color signifies blood

2 5 per cent aqueous solution of sodium bicarbonate
3 Iodine 2 gm , normal NaOH, 10 c c , and water 90 c.c
4 Acetone
5 0 1 per cent aqueous solution of basic fuchsin

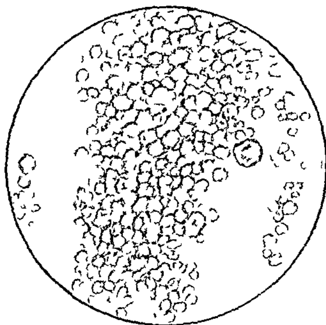
(These solutions keep for a considerable length of time and, for that reason, this modification of the stain has an advantage over the original use of anilin in oil gentian violet)

Technique A very thin smear is made of a selected portion of sputum upon a clean cover slip and passed through an open flame several times to dry and fix A few drops of the methyl violet solution are placed upon the smear and a smaller amount of the sodium bicarbonate solution added After about five seconds this is poured off and the iodine solution added and allowed to remain for an equal length of time It is then decolorized with acetone until no more color comes away after which it is washed copiously with water The counterstain is applied for a few seconds and washed off with water and the specimen is dried After mounting on a slide it is studied carefully under the oil immersion lens Gram positive organisms are stained deep purple, Gram negative organisms a light pink The predominant type of organism and the relative number and state of preservation of the pus cells should be noted and described

Stain for Tubercle Bacilli

A compact yellowish or mucopurulent mass of sputum is selected as free as possible from admixture with bronchial secretion, saliva, or mucus from the nose or throat With a platinum loop a small portion of this is spread in a thin even layer on a cover slip, and dried and fixed by passing it quickly several times through an open flame The smear is covered with carbol fuchsin (Ziehl Neelsen) solution and gently *steamed* over a flame for about four minutes It is washed with water and then decolorized by adding acid alcohol drop by drop until it is decolorized to only a faint pink, after washing with water It is decolorized further with 95 per cent alcohol for one minute and washed again with water It is counterstained by flooding with Loeffler s methylene blue for a few seconds and then washed with water dried and mounted Examination is made under oil immersion

Sources of Error Occasionally certain dyes will not stain certain strains of tubercle bacillus The best dye is Grubler s basic fuchsin



(*From Pelouze Office Urology W B Saunders Co*)

Fig 231 Prostatic secretion from a badly infected non draining gland The leukocytes are closely packed old and on the verge of disintegration Lecithin bodies are almost absent

7 Each ten minute specimen is examined immediately as to

a Volume

b Gross appearance Content of mucus blood, bile The presence of bile indicates regurgitation of alkaline duodenal secretions which will, of course, reduce the titratable acidity of the gastric secretion Since the trauma of passing a stomach tube and of continuous aspiration in many instances causes slight bleeding from the gastric mucosa, it is useless to do benzidine or guaiac tests on the aspirated material

c Free and combined titratable acidity—using Topfer's reagent and phenolphthalein as indicators The titration must be done immediately after collections since free acid on standing is converted to combined acid

Values for the Histamine Test

1 Normal 10 minute volume—15 to 60 c c

2 Normal total acidity—60 to 150° (1 degree equals 1 c c of 0 1 N acid per 100 c c of gastric juice)

3 All but 10 per cent of the total acidity should represent free HCl

4 Both volume and acidity of the secretion are decreased moderately in older individuals

Modified Histamine Test

In many cases quantitative data on the volume and acidity of the gastric secretion are not desired In such instances the fasting contents can be examined immediately for free acid and if present the test can be discontinued

If absent histamine is injected and a convenient time (20 to 30 minutes) is allowed for the drug to exert its effect The secretion is then aspirated and tested for acid

The presence of free HCl can often be tested by using the vomitus Its absence from the vomitus of course is not absolute evidence of achlorhydria, histamine stimulation must be used to establish the point

Stool Examination

1 If occult blood is sought the patient is put on a meat free diet for 3 days before collecting a laboratory sample

2 If a stool is to be examined for the presence of ova or parasites, it should be warm on arrival at the laboratory

3 If amebic dysentery is suspected and no parasites are found in the stool a sigmoidoscopic examination should be made and a direct specimen taken

4 When possible the physician should record the gross appearance of the stool

5 General Appearance—Two important findings are

a Tarry stools which indicate large amounts of blood

b The putty color which denotes the absence of bile The typical tarry stool is shiny jet black soft and sticky

Diet and medication may be responsible for abnormalities in color

6 *Occult Blood* Some gastroenterologists require three successive negative tests without a positive test over a period of three or four days before believing that blood is absent from the stool The guaiac or benzidine test should be applied only after a hemoglobin free and chlorophyl free diet has been given for at least four days The following foods should be excluded meat meat soups gravies, fish and raw green vegetables The regimen of milk and cooked cereal of the ulcer diet is ideal All iron or iodide medication must be discontinued for at least four days before the test If washing the teeth is followed by bleeding the mouth should be washed out until no blood appears so that none will be swallowed To demarcate the stools a charcoal tablet is given with the first meal of the restricted diet Several stools, including the first, which have been passed after the feces ceased to be discolored by the charcoal are examined Anorectal bleeding must be ruled out

BENZIDINE TEST

Wagner reagent 2 c c of a saturated solution of benzidine in glacial acetic acid 20 drops of 3 per cent of hydrogen peroxide A small portion of stool is taken on a spatula and smeared on a glass slide Reagent is poured over slide If the smear turns blue blood is

Consistency—Increased sediment when retention present. Increased mucus is found in catarrhal inflammations. The sediment particles should be small and uniform in size.

Blood—This may come from the mucous membranes of the stomach itself, from the nose, larynx, or gums or from a tracheobronchial or pulmonary lesions. Other causes are carcinoma, portal cirrhosis, chronic passive congestion of the stomach, peptic ulcer, gastric syphilis, acute gastritis, purpura hemorrhagica, acute anemia or aplastic anemia.

Organic Acids—Lactic acid commonly found with gastric retention and hypochlorhydria. All three are found in carcinoma of the stomach.

Enzymes—The absence of pepsin, rennin with achlorhydria suggests a true achylia found in pernicious anemia and in subacute combined degeneration of the spinal cord.

8 *Special Chemical Tests*

Strauss's Test for Lactic Acid—

Equipment: Separatory funnel marked at the 5 c c and 25 c c level.

Technique: Fill the funnel to the 5 c c mark with filtered stomach fluid. Add ether to the 25 c c mark. Shake for 15 minutes and let stand until the layers separate. Withdraw gastric juice by opening the valve in the bottom. Fill to the 25 c c mark with water and add 2 drops of 10 per cent solution of ferric chloride. Shake gently. A strong greenish yellow color indicates the presence of lactic acid (0 1 per cent or more). 0 05 per cent usually causes only a slight tinge of greenish yellow color.

Benzidine Test—

Wagner Reagent.—2 c c of saturated solution of benzidine in glacial acetic acid, 20 drops of 3 per cent hydrogen peroxide. To 10 c c of gastric contents add 3 or 4 c c of glacial acetic acid. Shake with 5 c c of ether. Let stand and pour ether solution over the Wagner reagent in a test tube. A blue color indicates the presence of hemoglobin.

Guaiac Test—

Guaiac Reagent—5 c c of fresh solution of guaiac in alcohol (1 part of guaiac to 50 parts of 95 per cent alcohol), 5 c c of 3 per cent hydrogen peroxide—mix and overlay gastric contents. A blue color at the point of contact indicates the presence of hemoglobin.

Histamine Test of Gastric Secretion

This test yields more reliable and consistent results than the Ewald or alcohol test meal method. The technique is as follows:

1 The patient fasts for at least 12 hours and is examined in bed under standard basal conditions.

2 A stomach tube is passed for a sufficient distance to allow its tip to reach the most dependent portion of the stomach. The patient is instructed to not swallow his saliva.

3 The fasting contents are aspirated by means of a 50 c c Luer syringe. This aspiration is continued until all residual food, previously swallowed saliva, respiratory tract mucus, etc., is cleaned out of the stomach. This specimen is usually unsuited for titration and is discarded.

4 *Continuous* aspiration is now begun and is carried on in ten minute periods until the volume of ten minute excretion has become constant. Usually two or three ten minute periods are necessary.

5 Histamine 0 5 mgm is injected subcutaneously. This may cause a general vasodilatation and even faintness. The continuous aspiration in 10 minute periods is continued until it is certain that the maximum histamine stimulation has occurred. This is reflected in the volume of gastric juice secreted. In no case is it necessary to continue for more than six periods and usually only three or four are required. The aspirated material should be clear or a slightly opalescent limpid fluid containing some mucus which can be removed by centrifugation.

6 Since proper continuous gastric aspiration is a procedure which is mastered only after practice, it should not be entrusted to a nurse but carried out by the physician himself.

Smear All cloudy fluids should be examined for organisms Cover slip preparations are made stained by Gram's method If the fluid is centrifuged and the sediment stained it is important that the centrifuge tube be thoroughly cleaned with cleaning fluid and rinsed well with water before using

TEST FOR TUBERCLE BACILLI

All available fluid is centrifuged at high speed for one hour The supernatant fluid is poured off, leaving about 5 c c in the centrifuge tube Enough 95 per cent alcohol is added to bring out a definite cloudy layer It is then centrifuged at high speed for 30 minutes Cover slip preparations of the sediment are made and stained for tubercle bacilli If a pellicle has formed it is carefully transferred to a glass slide, fixed with egg albumin and stained

Cultures Cultures from all cloudy fluids are planted on blood agar plates and on chocolate slants

WASSERMANN, GOLD SOL, TOTAL PROTEIN, SUGAR AND CHLORIDES

These tests must be made in special laboratories All remaining fluid is labelled and placed on ice or taken at once to the laboratory If a sugar determination is required, 2 c c of the spinal fluid are placed in a separate tube, labelled preserved with 1 drop of 10 per cent formalin and placed on ice

Bacteriological Procedures

Requisitions for bacteriological work must be filled out in full including diagnosis and the particular examination desired The name of the patient and physician must appear on the requisition This will facilitate the work and hasten reporting

Specimens must reach the laboratory fresh moist and if possible warm It is useless to send specimens to the laboratory when it is *closed for the day* *In order to care for emergency* culture work a small stack of the necessary media and an incubator are kept aside for this purpose The interne should be responsible for the proper planting of these cultures The following outline states briefly what examinations may be required

ROUTINE OF SPECIMENS

Blood Cultures Blood cultures must be taken with exceptional care to avoid contamination Most laboratories take blood cultures by direct inoculation of a flask of broth at the bedside The citrate method is only a little more trouble and yields a great deal more information

Ten c c of blood are removed, after being sure that the skin is properly sterilized with iodine and the blood is inoculated into a vial or flask containing 3 c c of 2 5 per cent solution of sodium citrate to prevent clotting In the laboratory, measured amounts (1 and 2 c c) of blood are pipetted into two Petri dishes, 10 c c of dextrose infusion agar are poured into one and 10 c c of blood agar into the other The remainder is pipetted into a flask of broth

Advantage of This Method

1 It enables the laboratory to inoculate the type of medium best suited to the isolation of any particular organism

2 It enables the bacteriologist to count the number of colonies per c c of blood giving a quantitative estimate of the degree of bacteremia

3 More rapid identification of the organisms can be made from the type of hemolysis and appearance of the colonies when they grow out on the surface of the agar

CHOICE OF MEDIA

Routine

Tryptose phosphate broth
Dextrose infusion agar
Blood agar (hemolytic strept identification)

Gonococcus, Meningococcus, Streptobacillus Moniliformis — The addition of 30 per cent ascitic fluid or chocolate agar is recommended

Brucella Abortus—Isolation difficult, but 2 per cent tryptose broth and agar are recommended by Huddleson Duplicate cultures should be set up aerobically and in a jar with 10 per cent carbon dioxide which is necessary for the growth of *B abortus bovis*

present Pus and usual foods and drugs do not interfere with this reaction—"negative" and "slight trace" reports are significant because of their delicacy

GUAIAC TEST

Reagent 5 c c of 1 to 60 solution of guaiac in 95 per cent alcohol 5 c c of 3 per cent hydrogen peroxide An emulsion of feces is made with water and the fats extracted with an equal portion of ether The ether is discarded and the reagent layered over the watery extract of stool A blue ring at the point of contact indicates the presence of hemoglobin False positives may be due to presence of pus copper iodides, bromides or iron

Thoracic, Pericardial, Abdominal and Joint Fluids

GROSS EXAMINATION

Record the

1 Amount (in cubic centimeters)
2 Color (clear, straw, brown, etc)
3 Odor (foul, etc)
4 Consistency (e g , gelatinous, thick or thin)
5 Bloody, purulent, etc

SPECIFIC GRAVITY

This should be taken at once before a pellicle forms or coagulation takes place As it usually cannot be done at once the individual obtaining the specimen should place a 20 c c sample in a test tube containing a large pinch of potassium oxalate crystals and mix well

CELL COUNT

The oxalated specimen is shaken thoroughly before the cell count is made Unna s polychrome methylene blue (filtered) is drawn into a red counting pipette up to the 1 mark and the specimen of fluid to the 101 mark after shaking the mixture the counting chamber is filled Under high power a differential and a total count of all cells in two large corner squares (1 mm x 1 mm) are made and the result multiplied by 5 This gives the total number of each type of cell per cubic millimeter

SMEARS

A few loopfuls of centrifuged sediment are placed on a cover glass and allowed to dry by gentle heating It is stained with Gram's stain and a search made for organisms

A search is made for tubercle bacilli on a smear of a centrifuged specimen stained by the Ziehl Neelsen method

CULTURES

Routine cultures are planted on a blood agar plate, a chocolate slant and in a broth tube

PIG INOCULATING

Several cubic centimeters of sterile material are placed in a sterile test tube and delivered to the Pathological Laboratory for inoculation into guinea pigs if this seems advisable

Examination of Cerebrospinal Fluid

GROSS APPEARANCE, COLOR, AND TURBIDITY

Any turbidity or abnormal color should be observed in each of the three tubes In doubtful cases of xanthochromia the tube containing the fluid last drawn should be compared by daylight with distilled water A pellicle should be looked for in a tube left undisturbed for several hours

CELL COUNT

Unna's polychrome methylene blue (filtered) is drawn into a red counting pipette to the 1 mark and spinal fluid to the 101 mark and shaken This procedure colors the erythrocytes yellow and the white cells blue The dilution is disregarded Either an ordinary counting chamber in which 10 large squares (each 1 mm x 1 mm) are counted is used or a special one (0 2 mm deep, i e twice the usual depth) in which 5 large squares are counted A total and a differential count are made If there are many red cells present the cell count is of doubtful clinical value

Sources of Error Blood from trauma to the tissues may get into the fluid Fluid from the third tube will contain the least amount of blood from this cause

GLOBULIN TEST

If the amount of fluid is small the Pandy test should be used since it requires only 1 drop of spinal fluid

enough concentrated NaOH to give a final concentration of 4 per cent This is allowed to digest in the incubator with occasional shaking for an hour or two then spun down at 2500–3000 r p m for 30 minutes the supernatant liquid is discarded and the sediment neutralized with normal HCl using phenolphthalein as indicator *For the antiformin method see page 1133*

Sputum Smear and examine for

a Tubercle bacilli
b *Spirochetes and fusiform organisms*
c Pneumococcus
d Streptococcus
e Charcot Leyden crystals Curschmann s spirals
f In asthmatics look for eosinophils

Culture on Blood agar or other suitable media For yeasts or fungi use Sabouraud s media

THROAT CULTURES

When throat cultures are taken in the presence of a membrane an attempt should be made to secure a piece of the membrane A swab moistened in sterile broth should be used and both tonsillar fossae and the posterior pharyngeal wall thoroughly swabbed taking great pains to avoid touching the tongue or teeth The swab is returned to the broth and sent to the laboratory at once In making cultures in a suspected case of diphtheria *separate swabs are taken from no e and throat* Cultures for meningococci should be taken *from the nasopharynx preferably* with a bent wire swab and planted at once on warm media such as ascitic blood or chocolate agar

Smear and examine for

a Diphtheria
b Streptococcus and related organisms
c Stain for eosinophils

EYE CULTURE

Same as for throat routine, and a smear and culture for G C

NOSE CULTURE

Same as for throat routine

STOOL CULTURES

Stool cultures must be fresh and warm An old stool specimen is useless Unless contra indicated a specimen should be obtained after a saline purge or enema

Culture Culture is made from a dilute suspension *and directly from stool specimen*

Examine By smear hanging drop for *ameba, ova and parasites preferably on a* warm stage

Media Desoxycholate agar and desoxycholate citrate agar (Leifson s media for general work) Wilson and Blair's bismuth sulfite agar for typhoid S S Agar for dysentery organisms and entameba medium for amebiasis

Note The above media have supplanted the endos and eosin methylene blue agar previously used

PUS

Pus should be sent to the laboratory in a sterile tube If there is any danger of its clotting *a flask containing citrate should be used* The type of infection suspected should be noted on the slip

Anaerobic Culture Blood agar

Aerobic Culture Blood agar glucose agar trypose phosphate broth plant gonococci on chocolate agar and special media

Smears Gram stain and acid fast stain

Gonococcus Cultures In good hands the cultural method is far superior to smears However smears should be made in every case The material can be planted at the bedside on the warm media and the plates then returned to the incubator immediately Incubate at 35 C under partial CO atmosphere In the Out Patient office the material should be kept cold and moist and sent to the laboratory *within a few hours* Swabs should be *planted in a small amount* of broth or ascitic fluid *and kept in the ice box until* the clinic is over

PLEURAL EXUDATE

1 *Smear* An examination should be made for pneumococcus staphylococcus streptococcus *and other bacteria*
2 It should be centrifuged and examined for tubercle bacilli and *injected into* a guinea pig
3 Cultures should be made anaerobically, aerobically and for tubercle bacilli

Gas Gangrene, Puerperal Sepsis — At least one flask and plate should be incubated anaerobically, since anaerobic organisms invade the blood stream at times particularly in these conditions

Suspected Gonococcemia, Meningococcemia, Subacute Bacterial Endocarditis — Cultures are incubated under partial carbon dioxide tension with a candle jar or with B subtilis cultures in the jar

When Previous Cultures Negative in Suspected Bacteremia—Incubate under partial carbon dioxide tension

TIME PERIOD OF CULTURES

Hold all routine cultures at least 10 days

Cultures in suspected cases of subacute bacterial endocarditis, undulant fever, meningococcemia gonococcemia should be kept at least three weeks before being discarded as negative

CULTURES FROM PATIENTS RECEIVING SULFONAMIDES

Although such fluids frequently become sterile cultures may be negative when viable organisms are present because of a marked in vitro bacteriostatic effect of the drug present in the inoculum To overcome this para aminobenzoic acid can be added to all routine culture mediums in a concentration of about 5 mg per 100 c c during their preparation and will withstand autoclaving at a pressure of 15 pounds for twenty minutes

BLOOD AGGLUTINATION TESTS

Blood is withdrawn from the vein in the same manner as for blood cultures It is then placed in a *sterile* test tube *without anticoagulant* and immediately taken to the bacteriological laboratory When both blood culture and agglutination tests are desired 10 c c of blood should be withdrawn and the first 5 c c placed in anticoagulant for culture and the second portion placed in a dry sterile test tube

COMPLEMENT FIXATION TESTS

1 Wassermann
2 G C comp fixation test
3 Complement fixation test for amebiasis

PARASITES—FILARIA

When search is to be made for these, the laboratory should be consulted beforehand as special technique is necessary Filaria, for example may be searched for in a wet preparation

URINE CULTURES

From females sterile catheter specimens should be obtained, from males, either sterile catheter specimens or specimens obtained after very careful cleansing of the meatus and after the patient has already voided a sufficient quantity of urine to wash away contaminants Such patients should void directly into the sterile tube Urine cultures should be kept in the ice box and sent to the laboratory promptly so that an accurate estimate of the degree of infection can be obtained Culture should be checked with Gram stains from the sediment of freshly voided urine

SPUTUM CULTURES

In collecting sputum for any type of culture it is best to supervise it personally For pneumococcus typing the patient should rinse his mouth with water and then cough One should be sure that he does not spit out aspirated nasal secretion but really brings it from the lungs If no sputum is obtainable several procedures may be tried

1 The patient coughs and the physician swabs off the mucus on the post pharyngeal wall
2 A culture is taken from the nose with a moistened swab
3 The lung is punctured over a consolidated area with a 20 gauge needle and a little exudate aspirated
4 The urine is tested against type specific sera for positive ring test due to the reaction of a specific soluble substance with specific antibody

When hunting for tubercle bacilli concentration may be tried on sputum collected for 3 days A bottle should be kept in a cold place and sputum added to it every 12 to 24 hours If this fails the fasting stomach should be washed out with some saline the first thing in the morning and the washings concentrated One method of concentration consists in adding an equal amount of NaOH (4 per cent) or

phytic companions Placing the swab in a tube of broth is a good policy, providing the material can be kept cold *Swabs should never be dipped in saline* since it is quite toxic to most organisms The bottom of the test tube can be filled with blood agar on which the swab is then allowed to rest

Specimens should be maintained at a temperature just above freezing during their transport to the laboratory This is particularly true of stool specimens in which an overgrowth of colon bacilli at room temperatures will obscure the presence of the pathogens sought for

Method of Examination for Parasites

FECES

Specimens following the ingestion of oil barium or bismuth are unsatisfactory

Collection of the Specimen

It is well for the patient to void before taking a sample of feces which should be collected in a clean dry container Fluid stools more often contain vegetative forms while formed stools contain cysts Blood streaks should be studied Bile salts given the day before by mouth may aid in finding amebae When they are sought the specimen must be kept warm and moist during the entire examination Several examinations may be necessary, as protozoa are notoriously irregular in making their appearance in the feces

Protozoa A drop of fecal emulsion is mixed with a drop of iodine solution covered with a cover glass and examined The action of the flagella is retarded by the iodine so that they can be better seen The nuclei of cysts are stained yellow Flagella should be examined by dark field illumination A small amount of the specimen is *emulsified* with normal saline solution and examined directly on a slide under a cover glass

Concentration of emulsified feces is said to be a better method The sample is filtered through several thicknesses of gauze and centrifuged for 15 seconds after which the sediment is examined on a slide and the remaining sediment is suspended in zinc sulfate solution in a test tube and more solution added until the tube is full and a convex meniscus is formed at the top This is set aside for 30 minutes A glass slide is gently touched to the meniscus in order to transfer to it some of the floated material which is then covered with a cover glass and examined

Sedimentation of emulsified feces in a tall container is the method used in looking for the heads of worms or for smaller ones such as hookworms After allowing to stand for 30 minutes the supernatant fluid is examined and discarded The sediment is then given a thorough study

Brine Flotation A particle of feces is emulsified with salt solution and then poured into a wide mouthed bottle so that the meniscus reaches a glass slide laid across the top The slide is left in this position for one hour It is then carefully removed and the adherent material examined Operculate ova and larvae will not float

Cedar Oil Preparation This is of value when one desires to preserve the specimen A thick smear of fecal sediment is allowed to dry at room temperature and then mounted in oil and examined Protozoa are injured by this technique

Hookworm Count (Ova) To 3 gm of feces sufficient N/10 NaOH is added to make exactly 45 c c This is shaken for a minute to make a fine emulsion, small beads being used if necessary With a pipette exactly 0 15 c c is placed on a glass slide and covered with a No 2 cover glass measuring 22 x 40 mm All ova are counted by means of a mechanical stage under low power The sum is multiplied by 100 to get the number of ova per gram of feces The total number of hookworms in the patient is determined by dividing the number of ova per gram of feces by 22

SPUTUM

Endamebae, flukes flagellates and echinococcus should be looked for The parasites are examined directly under the microscope or the sediment studied after centrifuging

URINE

It is important to avoid fecal contamination After centrifuging, the sediment is examined for microfilariae *F echinococcus* flagellates and *Schistosoma haematobium*

When indicated a specimen should be sent to the pathological department for sections

SPINAL FLUID CULTURES

For the ordinary pyogenic organisms or tubercle bacilli a sterile tube containing several c c of spinal fluid is sufficient Whenever the meningococcus or influenza bacillus is suspected, spinal fluid should be allowed to drop directly from the needle on to several slants of chocolate and blood agar which have been warmed to body temperature These should be taken to the laboratory as soon as possible and kept warm in the meantime Chocolate agar is the best single medium as it is about the only one on which all the organisms (except the tubercle bacilli) which cause meningitis will grow These cultures should be incubated in an atmosphere of 10 per cent carbon dioxide

1 Fluid should be centrifuged and smears made for tubercle bacilli and meningococci
2 Culture Blood agar, tryptose phosphate broth special media for tubercle bacilli injection into a guinea pig, colloidal gold, Wassermann, cell count, globulin and protein

ASCITIC FLUID

Same as for pleural fluid

TISSUES

Specimens of tissue for cultures nodes tonsils, etc , should be sent in a sterile tube or Petri dish to the laboratory

SMEARS

Smears give tentative indications of the type of infection in a few minutes whereas cultures take at least 18 hours also they show the proportion of the various types of organisms present as well as the cellular reaction in the exudate Smears are particularly useful in the examination of exudates from sites normally sterile such as serous cavities subarachnoid space and tissues and in cases of peritonitis and empyema, because cultures in these conditions often fail to reveal a growth

1 *Throat Smears* These are extremely unreliable in the diagnosis of diphtheria and various forms of tonsillitis One should be guided by the clinical appearance and by properly taken cultures for confirmation They are very useful in confirming a diagnosis of Vincent's infection of the throat
2 *Sputum* The gross examination of the sputum in conjunction with examination of a stained smear may yield valuable information especially in cases of Friedlander's pneumonia, lobar pneumonia and tuberculosis
3 *Urethral and Genital Smears* These are very useful from one who normally has a sterile urethra Those from the cervix however, mean little unless frank pus is seen Smears of urinary sediment are often more valuable than cultures, when the latter are made by simple broth inoculation
4 *Inflamed Joint and Cerebrospinal Fluid* These are of value in medical cases but are of little value in traumatic conditions Smears of meningitic spinal fluid may be very confusing The Gram positive cocci can be readily seen, but the Gram negative meningococci may be difficult to find The most common form in children is that due to the Pfeiffer bacillus They are frequently mistaken for meningococci because they may appear as Gram negative diplococci If this is suspected, smears should be stained with safranine for from five to ten minutes since they take stains with difficulty With this treatment the organisms will appear as quite small pleomorphic Gram negative bacilli and cocci They are often paired Their early identification is essential since specific rabbit serum therapy offers much hope in this highly fatal disease

Methods of Taking Cultures

If a high percentage of positive cultures are desired intelligent cooperation must exist between the physician and the laboratory Swabs must be taken from the lesion in question and with as little contamination as possible This is imperative in throat cultures

Swabs must be kept moist and planted as soon as possible because most pathogenic organisms die more quickly than their sapro

TETANUS

Indications	Standard Course	Duration of Immunity	Revaccinations
F those exposed t the da ger of petting or cru h g wound uch as m ary person l p o vid g t ey e perm ently tagged so that t s d in tead f a toxin w ll t g n case f in ry	A m P ecip tated T d (Na y method) 2 doses dmin t ed by tran scu ection t t les than 4 or m t n w k ntervals B th doses 0.5 c	I ef b t pr ged	A boost dose f 0.5 c.c Alum Ppt. to o d is routin ly gi en year fter the initial ourse This is repeated there ft t i terv s f 4 years fter th 1st boost r Emerg ency booster doses of 0.5 c.c e gi en under th f Lowing ircumstances 1 On mo th befor enter ng th ombat zone irrespective of the tim interv l sinc the previous i jection 2 A soon as pos ble after ering a wound or severe b rn n battle a punctured o lacerated non battle wound, powder burn o th s inj ry pos ble contaminated w th t t spores o bacil 3 Upon un ergoing sec ndary operativ interferenc or open manipulation when co tamination with tet nus organ sms is lik ly

R act Usually som muscle soreness and w ing
Ide f tion T g After th sec d dose f t e initial immunization f tetanus to d die tamp th identi tion tag w th cap tal "T" f lowed by th n mbe f th m th d th la t two dig ts f t e year e.g T 4 44

YELLOW FEVER

Indic ti ns	Method f Adm n tr ti	Expected Duration f Immun ty	Revaccinations
All personn l t e duty n or about to be transferred t t rough eas wher t da ger of y low fev r ists S ch areas exists in Asia Afri a, S America nd the Southwest Pacific Immu izatio f in f nts nd 1 year of g not ecommended at p esent	1 dose f 1 10 d l tion f n centrated h ng atten ted irus ac in in normal l dminist red subcutaneou ly Th d ted a cin must be sed w th 3 hours it hould t be gi en oncurrently w th smallpo c tio o when the person suffering from irus d a	2–4 years	Booster doses of 0.5 c. ubcutaneously is routinely given t int rv ls f 3 years Emer gency booster 1 0.5 .c. is given in th p esence of n ep demic

Re ction Very infre ently slight temperature rise or headach bout 5 t days fter injection

EPIDEMIC TYPHUS FEVER

Indicatio	Method f Admini tratio	Duration of Immunity	Revaccinations
All personn l t d ty in bout t be tran ferred t o through areas where da ger of epidemic typh ist S h eas exists E rope Asia Africa and S Am ic NOTE Cent l, South d Southwest Pacin ea not incl ded	3 doses f 1 0 c h d ministered by subcutaneou injectio t intervals of 10 d ys	N t m re th n 6–8 months No protec t on is afforded g inst "endemic or "scrub" typhus	Booster doses of 1.0 c.c s bcuta eously is given routinely t 6 month interv ls while in th bove rea therwise potentially exposed

Re c N serious eactions h bee reported

CHOLERA

I dicatio s	Method f Administration	Duration f Immunity	Rev cin tions
All pe nn l t e d ty in bout t be t ansferred t or th ugh as wh d g f h ier exists S h ea ist in Egypt th Nea East, Asia nd th So thwest P ifi ex l s f Austra nd New Zealand	2 d ses the first 0.5 c.c., t 2nd 1 0 c administered subcu t eously t int rv ls f 7 10 d This cin may be g e ncurrently w th ty ph d m It contains 8 000 milli bacil d ib ies p c	6–1 m ths	Booster dose f 1.0 c.c. ubcu taneou ly is outinely gi en at int rvals f 6 month while in t bov eas or erwise po ential y e posed

Re ctio N se ious h bee epo t d

BLOOD

The characteristics of the disease in question should be carefully considered with regard to the optimum time for seeking the organisms in the peripheral blood stream Eosinophilia or the finding of Charcot's crystals may be suggestive of parasites For the best results an oil immersion lens should be used In seeking malarial parasites blood is obtained from the finger just before a chill Smears, both thick and thin, should be made using either Wright s or Giemsa s stain More parasites may be found if adrenalin is given 30 minutes before the blood sample is taken It is unlikely that any malarial parasites will be found after anti malarial treatment such as quinine has been taken for some time When filarial parasites are being sought the larvae of microfilariae should be sought A drop of blood is obtained from the finger and examined under a cover glass A smear should be made and stained with Giemsa's stain If this proves fruitless, a larger amount of blood from the finger should be taken and laked with 2 per cent acetic acid in a small centrifuge tube, centrifuged and the sediment examined under a cover glass In cases of suspected relapsing fever fresh capillary blood should be examined directly under the microscope and a smear also made with Wright s and Giemsa's stains If these are negative a mouse should be inoculated with 0 3 c c of blood and its blood examined every two days for two weeks

Immunological Procedures

The immunological procedures hereinafter described follow closely those advised by the United States Public Health Service and where practicable are those used by our armed force

SMALLPOX

Indications	Standard Course	Expected Duration of Immunity	Revaccinations
Ad is d for all infants before 3 months of ag Should be re qu red sho tly b fore entrance to school and certain employ ments and before fore gn t a el for those de t ned fo or sta t oned in Afr an Eu opean and Near Easte n ar as who ha e not been vacci ated ga st smallpox w thin the pr io s 6 months	1 dos pressure method using the side of the needle point 30 times within a 3 mm a ea at the in se ti n of the delto d muscle	1 5 yrs	At l st e ery 5 years and at any t me when the e is dang r of exp su e For ome p ona l groups a general c nation e ry 5 years is the most effic ent procedu e

Reaction A *Immune reaction—o cu s n a fully protected nd idual Erythema reache ma imum in from 8 to 72 ho rs o v s culat on o u s as a rule*
B *Accelerated e ct on—o cu s in pa t ally p ote ted ind duals The eryth ma re he a maximum in 4 to 7 day esi ula tion is usual*
C *Prim ry r action—occurs n a u prot ted ind dual Erythema reaches a ma imum in 8 to 14 d ys esicul t on always occurs*

TYPHOID AND PARATYPHOID FEVERS

Indications	Standard Course	Expected Duration of Immunity	Revaccinations
Ad ised o ly fo cond t on wh re sa ta ion is uncertai not fo us al city dwellers Ad sed for fore n travel	Triple a e ta ng 1000 m ll on typho d 250 m ll o e h paraty pl id A and B t m G e 3 d by ub itan o s inj c ti t i te l f to 10 days F t do e 0 5 c S ond dose 1 0 Th d do 1 0 c c	*3 months to 3 yea s*	E h ea foll w ng the f t stand d ou s r ut e 0 l c b t nt a t neou ly Repeat th bo t r hene in e ed p t c pated p t t fr m th p u do s i d ubt If o y l bo t g ven r peat th tanda d ft r 3 y a s

R a t ons F equently ca ses local d scomf t a d occ i ally a m ld feb le r ct o

[illegible]

Schick Test Diphtheria	Culture filtrate heated to inactivate toxin	A person immune to diphtheria has so much [illegible] antitoxin in the blood and tissue juice that any injected diphtheria toxin cannot reach the antibodies fixed on the tissue cells and accordingly a negative reaction results. If the antitoxin is deficient the fixed antibodies are attacked and a positive reaction results. Always use control
Dick Test Scarlet Fever	Culture filtrate heated [illegible] the toxin	Due to hypersensitivity to bacterial protein in the culture filtrate. No [illegible] needed. Common error is to call a slightly positive reaction negative
Schultz Charlton Scarlet Fever	Scarlatinal antitoxin	Blanching within 6 to 24 hours diagnostic. Use controls

The test remains positive for many years after infection whether clinical or subclinical. Thus its value in diagnosis [illegible] to the frequency of exposure to the infection. Negative tests are of [illegible] value in excluding infection.

REMARKS CONCERNING SKIN TESTS

The tests that depend upon the toxicity of the test substances are the Schick and Dick tests for the detection of susceptibility to diphtheria and scarlet fever A measured amount of toxin is injected into the skin In a susceptible subject an indurated reddened and painful lesion is seen in three days in the Schick test and an area of erythema in 24 hours with the Dick test If the subject has a level of circulating antitoxin arbitrarily considered sufficient to protect him from the disease the injected toxin will be neutralized and no reaction will result These tests may be misleading particularly in adults for in a person previously immunized by injection of or contact with the offending organisms there may be little circulating antitoxin but the cells may possess the ability to elaborate antitoxin very quickly in response to a slight stimulus Accordingly a few weeks following a positive Schick test it is not unlikely for the repeat test to be negative because the test injection has stimulated the production of antitoxin The Schultz Charlton test is the reverse of the Dick test In this test scarlatinal antitoxin is injected into the skin of a patient with a suspected red rash If blanching appears at the site in twelve hours the rash is considered scarlatinal

Serologic Tests of Proven Diagnostic Value

PRECIPITATION TESTS

1 *Syphilis* Hinton Kahn Kline Eagle and Mazzini tests These tests are very useful since their ease of performance and high sensitivity make them ideal for the diagnosis of syphilis

2 *Parasitic Infestations* In trichiniasis and echinococcal disease the patients usually develop a high titer of precipitins as well as positive skin tests

3 *Pneumonia* A test for the presence of the capsular polysaccharide in the blood and urine may be a valuable guide to prognosis and thus to therapy While this is true the tests are little used

4 *Spinal Fluid* A ring at the interface between spinal fluid and influenzal or meningococcal antiserum indicates meningitis with the corresponding organism

5 *Anthrax* This may be diagnosed by the Ascoli test

AGGLUTINATION TESTS

1 *Brucellosis* Agglutinins when present in titer of 1 80 or more are usually significant The test is often negative in chronic infections or it may be positive in normal subjects in endemic areas particularly after acute infections

Ref Am Jour Med Sc 197 646–653 1939

2 *Tularemia* Agglutinins nearly always rise usually to high titers and persist for many years

3 *Pneumonia* Agglutinins are considered by many to be the most satisfactory method for titrating antibodies

Ref Finland Maxwell N Eng Jour Med 218 1033–1044 1938

PLAGUE

Indications	Method of Administration	Duration of Immunity	Revaccinations
All personnel on active duty in or about to be transferred to or through areas where danger of plague exists. Such areas exist in S. America, Africa, Near East, India, Burma and China	2 doses given subcutaneously at intervals of 7-10 days. The first dose is 0.5 c.c., the second dose is 1.0 c.c. The vaccine contains 2,000 million killed *bacilli per c.c.*	4-6 months	Booster dose of 1.0 c.c. subcutaneously is routinely given at intervals of 4-6 months while in the above areas or otherwise potentially exposed

Reactions: None serious have been reported.

DIPHTHERIA

Indications	Standard Course	Duration of Immunity	Revaccinations
Advised for all children by 6 months of age	Alum Precipitated Toxoid: doses (1 c.c. or 0.5 c.c. as indicated on the package) about 4 weeks apart subcutaneously. Plain Toxoid: 3 doses of 0.5 c.c., 1.5 c.c. and 1.0 c.c. subcutaneously about 3 weeks apart	About 5 years as r ted by stimulation such as association with urban population where diphtheria carriers are numerous	Another dose advised on entering school

Clinically Important Skin Tests

Condition	Test Substance	Remarks
	Immediate Hypersensitive Reactions	
Asthma, Hay Fever, Food Allergy, Serum Sensitivity	Extracts of pollens, foods, extracts, serum	Some patients are skin sensitive without symptoms
Helminth Infestations: Trichina and echinococcal disease	Extract of worm or their polysaccharides	In trichinasis delayed reaction first is replaced (14-70 days) by an immediate reaction
	Hydatid fluid aspirated and injected intradermally causing a white papule. In a positive e ct on the papule increases. In a negative re t on it s absorbed in a few days	
Pneumococcic pneumonia (Francis test)	1:10,000 dilution of capsular polysaccharide of infecting type	As soon as the test becomes positive all therapy stopped whether serum or drugs or both have been used
	Delayed Hypersensitivity Reactions	
Tuberculosis	Old tuberculin. P.P.D. is better (Mantoux Test)	A positive reaction may mean the presence of viable bacilli in an active or latent infection or of a healed infection with viable bacilli absent. A negative reaction is strong evidence against the presence of a tuberculous infection unless one of the following conditions exist: Miliary T.B., fulminating T.B., measles and certain other acute diseases
Brucellosis	Brucellergin, brucella vaccine	Many false positives and negatives. The test may increase the titre of antibodies blood in the patients and may thus aid in the diagnosis
Tularemia	Foshay detoxified vaccine	Value in that it becomes positive early in the disease. Do not inject antibody which reacts with circulating antigen to produce a wheal. Test remains positive for years after recovery from disease
Lymphopathia venereum (Frei Test)	Inactivated bubo pus, infected mouse brain or inactivated chick embryo extract	The last mentioned material is the most satisfactory and is available commercially
Chancroid (Dmelcos Test)	Vaccine (Ducrey's bacillus)	Intradermal injection for diagnosis

D t Tox R a t ns

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4 *Dysentery* Agglutinin titer seldom rises high Occasionally an agglutination test is useful when positive stool cultures are not obtained Tests with the Sonne and Shiga types are quite specific the Flexner group is antigenically heterogeneous

5 *Salmonella Infections* In this group agglutination tests are of great value There are an extraordinary number of antigens in the group A properly performed Widal test should include the various organisms that cause enteric fever in the local area in question

Other Diseases Other diseases in which agglutination tests are being done are

Asiatic Cholera
Bacillary Dysentery
Epidemic Meningitis
Glanders
Paratyphoid Fever (after 7–10 days)
Plague
Typhoid Fever (after 7–10 days)
Undulant Fever (after 7 days)
Weils Disease (after 6 days)

WEIL FELIX REACTION

This is really an application of the Widal agglutination method to the diagnosis of rickettsial infections such as typhus or Rocky Mountain Spotted Fever The rickettsia causing these diseases are difficult to work with It was discovered empirically that the serum of patients having one of these diseases will agglutinate certain strains of non pathogenic proteus bacilli Agglutinations which occur in dilutions of 1 80 are suspicious dilutions of 1 160 are positive The usual positive reactions for the three proteus strains are as follows

OX 2 This proteus strain is agglutinated more or less equally by several rickettsial diseases

OX 19 Strongly agglutinated in classic epidemic typhus tabardillo endemic typhus of the United States

OX K The Kingsbury strain is strongly agglutinated in tsutsugamushi fever and in the scrub typhus of the East Indies

Undependable Reactions

These are seen in

1 Spotted Fever
2 S African Typhus
3 Tick bite Fever
4 Sao Paulo endemic typhus
5 Febbre erruttiva
6 Fievre boutonneuse

INFECTIOUS MONONUCLEOSIS (HETEROPHILE AGGLUTINATION TEST)

This agglutination test is used in the diagnosis of infectious mononucleosis It has been found that the serum of patients with this disease (or with serum sickness) will agglutinate sheep red cells in high dilutions the serum of normal persons will not do this This may also be associated with a false positive serologic test for syphilis

Ref Am J Med Sc 183 90–104, 1932, 196 79–83 1938

TYPES OF AGGLUTINATION

H' or Flagellar Agglutination This is due to sensitization of the flagellar antigens It is rapid (2 hours at 55 C) and large floccules are formed

O' or Somatic Agglutination This is due to sensitization of the bacterial bodies It requires from 6 to 12 hours at 55°C and fine granular masses are formed

To detect O agglutinins either a non motile strain or a specially prepared suspension treated with heat to destroy the H antigen must be used O agglutinations are very important in doubtful cases because although a high H agglutinin titer may be produced by prophylactic vaccination or the anamnestic reaction O agglutinins seldom appear above a titer of 1 80 except in response to infection when they usually parallel H' agglutinins

COMPLEMENT FIXATION TESTS

Complement fixation is of great importance in the diagnosis of syphilis It is used in the following diseases

1 *Syphilis* The Kolmer Wassermann Test

2 *Gonococcal Infections* This test is much abused Antibodies appear only infrequently in response to local genito urinary infections, but they do appear in a high percentage of cases in endocarditis and arthritis The test is useless in following the course of local gonor

rhea it may be positive in salpingitis It may be useful in the differential diagnosis of arthritis and bacterial endocarditis

3 Many bacterial diseases result in the formation of specific third order immune bodies which make complement fixation tests possible These tests are tedious and whenever possible the diagnosis of the disease in question is usually made by easier methods These diseases are

a Cysticercus disease
b Amebiasis
c Echinococcus disease
d Meningococcus infection
e Pneumonia
f Staphylococcus infection
g Streptococcus infection
h Trichiniasis
i Typhoid fever
j Weil s Disease

SEROLOGICAL DIAGNOSIS OF FILTERABLE VIRUS DISEASES

The diagnosis of these diseases is impossible in the ordinary laboratory It is important to collect serum in the acute stage of the disease and then at the optimum time for the appearance of antibodies usually from three to four weeks after the onset

Precautions in the Use of Sera—Skin Tests

Serum should never be given nor skin tests performed (Dick or Schick or any tests for the anaphylactic or immediate type of sensitivity) without having a syringe containing 1 c c of 1 1000 adrenalin ready for use

A patient should never be left alone after such injections and never allowed to leave the office or hospital until 45 minutes have elapsed after testing

Before Serum Administration The patient should be questioned carefully about allergic disease previous injections of serum and the reactions if any to them He is tested as follows

1 a One drop of normal horse serum diluted 1 10 or 1 100 is instilled into the conjunctiva If no reaction occurs in five minutes

b Inject 0 1 c c of this diluted serum intradermally with 0 1 c c of saline as a control at another side Positive reactions are itching of the eyes redness and lacrimation enlargement of skin wheal often with development of pseudopods which may occur in 15–30 minutes

2 Normal horse serum must be used for testing before using antipneumococcus serum because if the serum itself were used union of the circulating specific soluble substance with the injected antibody might give a false positive reaction Tetanus and diphtheria anti toxins may be used as such in testing

3 If serum is to be administered intravenously particularly antipneumococcus serum a small test dose is usually given (0 5–1 0 c c) very slowly to test for chill producing substances or sensitivity not brought out by the above tests The latter is indicated by *tachycardia and a fall in blood pressure of* over 15 mm of mercury during injection the former occurring by chills and fever within two hours

4 Serum for intravenous use should be warmed to body temperature and injected very slowly (about 1 c c per minute) with frequent observation of the rate and the quality of the pulse *Do not dilute concentrated sera with saline* as it will precipitate the concentrated globulin from solution Do not use sera that are not perfectly clean

5 Keep a record of the lot number of any serum on the patient s chart in case any reaction occurs later

6 The types of reaction that may occur are as *follows*

a *Immediate Anaphylactic Reaction* occurs in the first few minutes and is characterized by nausea asthma precordial and epigastric distress prickling urticaria syncope and collapse This may occur with a simple skin test and may end fatally Adrenalin 1 1000 should be administered immediately 1 0 c c subcutaneously or 0 3 c c intravenously Do not give more than this dose at once intravenously but the dose may be repeated very soon if no effect is obtained

b *Thermal Reaction* Chills followed by fever occurring within an hour or two of the intravenous administration of serum It is analagous to reactions to other types of intravenous therapy is not due to anaphylaxis and is not benefited by adrenalin

c *Accelerated Serum Sickness* Urticaria edema and fever occurring from a few hours to a few days after serum are usually due to previous serum administration

d *Serum Sickness* Fever, arthralgia, lymphadenopathy, urticaria and edema with the onset 6 to 10 days after the injection of serum

7 *Handling of Sensitive Patients* Certain commonly used sera are supplied commercially from more than one species If a patient is known to be sensitive to horse serum, it is better to try to obtain one of these other sera if possible

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Appendix

COMMON PROCEDURES AND DIETS

Common Procedures

THORACENTESIS

The site selected for tapping is usually the 6th–9th interspace in the posterior axillary line A large skin area is cleansed with iodine and alcohol The skin and subcutaneous tissues as far as the parietal pleura are infiltrated with 1 per cent novocaine

The best position of the patient is sitting up and leaning forward If however he is quite ill or if there is a possibility of syncope he should lie on the affected side with his under arm raised thus widening the intercostal spaces A large bore needle about 10 cm long is connected to a 50 c c Luer syringe A small incision is made in the skin with a sharp blade The needle is thrust through the incision and passing just above the rib margin (avoiding the nerves and vessels which lie in the groove at the lower rib borders) enters the pleural cavity when a sudden loss of resistance is felt Gentle suction is made with the syringe and the fluid aspirated To prevent air entering the pleural cavity a three way stop cock or rubber tubing which can be clamped off is attached to the needle When sufficient fluid has been removed for culture specific gravity etc the needle is connected to the rubber tube leading to the suction apparatus The rubber tube in turn fits into a bottle in which negative pressure is created by means of a suction pump When the needle is finally withdrawn the skin area is covered by collodion or a sterile bandage The cavity may be loculated then it will be necessary to repeat the puncture in several places before all of the fluid is found

It is not advisable in most instances to withdraw more than 1000 c c of fluid from the chest at the first operation Stop at once it cough severe pain rapid pulse or dyspnea occurs Complications are infrequent but may be present pneumothorax subcutaneous emphysema syncope pulmonary hemorrhage with hemoptysis or pulmonary thrombosis It is advisable to give the patient 15 mgm of morphine sulfate prior to the procedure especially if he is apprehensive

PERICARDIAL PARACENTESIS

Pericardial paracentesis is not without danger (puncture of coronary vessels or laceration of the myocardium) It should be done only when there is a real indication and after adequate consultation

The operation is performed similarly to thoracentesis The common sites are

1 Just outside the apex beat
2 In the chondroxiphoid angle
3 In the 4th or 5th interspace either to the left or right border of the sternum It is advisable to use a blunt needle

ABDOMINAL PARACENTESIS

The urinary bladder should be emptied immediately before this procedure The patient should be in a sitting posture on the edge of the bed The skin below the umbilicus is prepared with iodine and alcohol if it is hairy it should be shaved The usual site of the puncture is midway between the umbilicus and the pubic symphysis in the midline The skin and subcutaneous tissues as far down as the peritoneum should be infiltrated with 1 per cent novocaine The site is draped with sterile covers and a small incision made in the skin with a sharp scalpel A large bore trocar is pushed through the incision and by rotatory movements through the tissues until it enters the abdominal cavity The plunger is then withdrawn from the trocar and the strainer inserted

If after the first few c c have been removed the patient shows no ill effects the fluid is allowed to run until the abdomen is emptied as completely as possible when the trocar is withdrawn As there may be leakage of fluid from the incision a binder and pad should be applied over the area

INTRAVENOUS INJECTION OF FLUIDS

Indications

a) When there is urgent need for fluid or medication
b) When the amount of parenteral fluid is so great that it could not be efficiently absorbed by hypodermoclysis
c) When due to the condition of the patient, fluid cannot be taken orally
d) When the fluid is too irritating to be given by hypodermoclysis

Equipment Necessary

a) Murphy drip and stop cock to regulate rate of flow
b) 20 gauge needle
c) Tourniquet
d) Alcohol antiseptics and gauze for skin preparation
e) Adhesive tape to strap needle in place
f) Narrow board to rest extremity upon
g) Standard to hold flask hot water bottles to keep solution warm
h) Sterile rubber tubing with glass adapter or Kaufmann syringe

Technique

The veins usually selected for venipuncture are the median cubital or basilic veins of the arm the veins of the dorsum of the hand the anterior malleolar veins the external jugular veins or even varicose veins of the legs In infants the superior sagittal sinus is frequently used The superficial cutaneous veins on the hands or feet while conspicuous are thin walled and not being supported by areolar tissue tend to roll off the point of the needle A deep vein if palpable is easier to enter than a clearly visible superficial vein This is true of the anterior malleolar vein whose location is so constant that a needle can often be inserted into it even when the vein is neither visible nor palpable

Aseptic technique should be used in preparing the site of the injection In the case of a delirious patient it is well to immobilize the extremity and hold it in place on a board with bandages It is well to remove all air from the apparatus before giving fluids intravenously This may be done by raising both tubing and needle above the level of the flask thus forcing any air back into the Murphy drip A small amount of air entering the vein will do no harm It has been shown that large amounts of air have been introduced into dogs veins without causing any ill effects or air embolism

A tourniquet is applied to distend the veins If it is applied too tightly it will cut off the arterial supply and the veins will not be distended The tourniquet should be removed gently as soon as the needle is in the vein An arm cuff can be used to good advantage as a tourniquet

The point of the needle is inserted through the skin with the bevel down parallel and lateral to the vein so that the initial impetus of the needle will not carry it through the wall of the vein The needle is then introduced into the vein at an oblique angle Blood will be seen entering the glass adapter or Kaufmann syringe The tourniquet is now gently removed, the stop cock released or loosened as the case may be and the fluid permitted to flow into the vein The needles used are usually 18 or 20 gauge and should be sharp with a short bevel

After the needle is in the vein it may be found that a slight adjustment in its position is necessary in order to secure a satisfactory flow of blood This can be managed by placing a small piece of gauze beneath the glass adapter or Kaufmann syringe which will hold the needle in the vein at an angle of about 30 degrees The needle is then fixed in this position by narrow stips of adhesive tape placed across the end of the needle and the adapter and the rubber tubing

Much has been written about the rate of flow of intravenous solutions While the writer has never seen any ill effects from fluids given at a fairly rapid rate it can be said that under ordinary circumstances fluids should be given at a rate of about 120 drops per minute

Complications of Intravenous Therapy

1 **Extravasation of Fluid into the Tissues** This commonly occurs when the needle becomes dislodged from the vein through movement on the part of the patient improper fixation with adhesive tape of the needle and adapter or through undue manipulation of the rubber tubing when refilling the flask or adjusting the Murphy drip apparatus This

complication is of little concern when isotonic saline or dilute glucose solutions are used but a sloughing may follow an extravasation of fluids such as hypertonic saline or glucose or acid and alkaline solutions When it occurs the needle should be withdrawn and the affected parts massaged in order to disperse the fluid When injecting arsenicals or other solutions that may cause a slough if accidentally introduced outside of the vein it is a good precaution to have at hand a 2 c c syringe equipped with a fine hypodermic needle and filled with normal saline In the event of an extravasation of the injected fluid the normal saline is injected into the area and the part gently massaged This will prevent a slough and by dilution of the injected material stop any after effects such as burning etc

2 **Thrombosis of the Veins** This is particularly troublesome after repeated venipunctures If these are necessary the site of the puncture should be changed The solutions should be kept running slowly all the time to prevent collapse of the vein walls agglutination and blockage of the flow of fluid

3 **Chills and Fever Following Intravenous Administration** These reactions may be alarming but are rarely if ever fatal in the absence of other complications

HYPODERMOCLYSIS

Indications

a) When a patient is unable to take fluids orally
b) When a large amount of fluid is desirable without putting a burden on the heart

Fluids Used

Physiological saline or 3 per cent glucose in saline solutions

Contraindications

Hypodermoclysis is unsatisfactory in those with edema

Equipment Needed

a) Antiseptic solutions and gauze sponges
b) One 2 liter flask
c) Two needles of No 20 gauge
d) Three pieces of rubber tubing 30 inches in length
e) One glass Y connection
f) 2 stopcocks to control rate of flow
g) Standard to hang flask upon
h) Hot water bottled to keep fluid warm

Technique

Hypodermoclysis may be given into the thighs axillae or the abdomen Most physicians prefer the thighs One ounce of 1 per cent novocaine solution added to each 1000 c c of solution will reduce the patient s discomfort

With the patient lying flat in bed and the *knees elevated upon a pillow the anterior or* lateral aspects of both thighs are prepared with iodine and alcohol and draped with sterile towels It is a good practice to remove all air from the tubing since a small amount of air may block the flow of fluid or it may cause a harmless subcutaneous emphysema

The skin of the thigh is pinched between the thumb and fingers and elevated from its normal position to insure separation from the fascia The needle should never be introduced beneath the fascia The rate of flow will depend upon the patient s ability to absorb the fluid and is regulated by the nurse in charge Aseptic technique must be observed to prevent the development of infections If the fluid is given too fast pain will result If the needles are placed too high and are directed medially edema of the genitalia may occur and if they are introduced through the deep fascia into the thigh muscles or into the breast in a subpectoral infusion the pressure of the fluid may seriously hamper the local circulation of the blood and tissue necrosis may result

STERNAL BONE MARROW CAVITY ADMINISTRATION OF FLUIDS

Toscantins (14 15 16) in 1940 first described the introduction of fluids into the general circulation via the bone marrow The advantages are (1) it is convenient and rapid thus ideal for war time use (2) it is of value where because of burns or edema the vessels are inaccessible (3) when clysis is inadequate (4) it is of great use in restless or excited persons who may dislodge intravenous needles during periods of transportation or during periods of hyperactivity (5) it offers the only effective route for fluid therapy after all available veins have become thrombosed (6) in patients with circulatory collapse where time consuming dis

section may be required to place the needle in the vein, (7) to avoid thrombosis of veins in those requiring long continued fluid therapy

Anatomically, the sternum lends itself ideally for the administration of fluids The liberal venous drainage of the sternum consists of plexuses on both surfaces of the bone draining into the internal mammary vein of the same and opposite sides and thence to the innominate veins The thin table of compact bone is fairly easily pierced with a needle and the spongy character of the inner bone makes the entrance of fluid possible

The required equipment is a 10 c c glass syringe a B D Luer Lok special needle #458 LNR equipped with stylet, a hypodermic needle, and about 10 c c of procaine hydrochloride (1 per cent solution)

The area selected is the lower part of the manubrium or the upper part of the body of the sternum chiefly because the spongy layer of bone is thickest in this layer An intradermal wheal is raised with the procain solution and through it the needle is advanced to the periosteum which in turn is infiltrated with a small portion of the solution After a few moments to allow the solution to take effect, the sternal puncture needle is firmly inserted directly in the midline through the anesthetized area until firm contact against the sternum is felt The needle point is directed cephalad at an angle of about 30 degrees with the anterior chest wall In most cases a sudden diminution of resistance will be felt when the bony table is pierced and it will be noted that the needle can be turned or rotated when it is in proper position Also when properly placed about 2 to 2 5 cm of the shaft is beneath the skin surface The needle as a rule rests securely without further fixation Sterile dressings are used to cover the area After the needle is in place the stylet is removed and after attaching a glass syringe air and marrow contents are aspirated If the needle is placed correctly marrow elements and blood will be drawn into the syringe although such procedure is frequently accompanied with pain Sodium chloride solution can be run through the needle to clear it and the fluid container is then attached to the needle by sterile tubing The fluid to be transfused is allowed to run by gravity flow with the rate of flow adjusted to each individual case Severe coughing may cause a thin stream of blood to be ejected into the glass adapter attached to the needle but no alarm should be felt over this phenomenon

It is well not to allow the pressure in the tubing to reach too low a level as this will allow bone marrow elements to enter the needle and their speedy coagulation will block the needle Where this happens the recommended procedure to clean the needle is to insert and remove the stylet and then inject fluid under slight pressure This is not always successful and the needle may have to be withdrawn and reinserted in another location

Fluids such as whole blood plasma 5 per cent dextrose in saline, penicillin, and pentothal sodium in 5 per cent solution have been given with satisfactory results and the needle has remained in situ for periods ranging up to eight days

PLASMA TRANSFUSION

Plasma is the liquid solution of three important proteins viz albumin, globulin and fibrinogen The total protein content may vary from 6 5 to 8 5 gm per 100 c c Fibrinogen is concerned with the clotting of blood The other two proteins have as their function the maintenance of blood bulk and the stabilization of osmotic pressure so that an adequate balance between the plasma and the tissue fluids can be maintained in the capillary circulation Regeneration of proteins is a slow process by the organism Fibrinogen appears to be replaced promptly even after severe hemorrhage in from four to six hours Plasma is the ideal physiological fluid for the maintenance of blood volume The removed red blood cells are in no way effectual in exerting any colloid osmotic pressure this being the function of the plasma proteins and this property is useful in the use of stored plasma in cases where the blood pressure has fallen to dangerous levels

There are three types of plasma (1) *liquid plasma* (2) *frozen plasma* and (3) *dried plasma* Plasma is made by centrifuging freshly collected blood or by gravity sedimentation of whole blood stored in a refrigerator The use of a dextrose preservative solution is recommended if more than 5 day storage of whole blood is desired Methods of preservation of plasma are (1) storage in the liquid state at

room temperature with or without chemical preservative (2) simple desiccation (3) vacuum desiccation from the frozen state and (4) preservation in the frozen state

Preparation

500 c c of blood are drawn from the donor and a small amount placed in a pilot tube which is used for typing and study of the serologic reaction The blood is then centrifuged and the plasma placed in 2000 c c pooling bottles Cultures and total protein determinations are taken and some inject a small amount of merthiolate to the plasma as a preservative It is next dispensed into 250 c c plasma vacs If liquid plasma is the desired end product it is stored at room temperature *never in the ice box* If frozen plasma is desired it is placed in a freezing chamber and frozen rapidly and then maintained in storage at a safe temperature below freezing When needed it is thawed rapidly in a water bath at 37°C with occasional gentle agitation Vacuum desiccation from the frozen state and the preservation in the frozen state are the methods preferred for prolonged preservation Recent studies at the Army and Navy Medical Schools have demonstrated that the liquid form kept at room temperature has a safe storage period of two years The temperature should be held between 60 and 80°F with allowable maximal limits of 55 to 100°F With this form of storage there is a rapid loss of prothrombin and complement and a slow loss of antibody content but these changes do not interfere with the value of the plasma in the treatment of shock It has been shown that plasma stored in the frozen state remains practically without change during storage The official limit of storage at +5 to −4 F is at present 3 years Many feel that this is a conservative estimate and that there is every reason to believe that plasma can be stored indefinitely within this range of temperature The dried form can be stored safely for five years The dried form is the form of choice of the armed services It can be stored anywhere provided the package is not allowed to freeze or is not exposed for long periods to temperatures above 130 F In the Army Navy package each unit is complete with distilled water for reconstitution and an administration set and thus can be used in the field without regard to hospital facilities *Dried plasma offers no advantages for general hospital use*

Administration

A double transfusion set with a stainless steel filter is used It can be run in with 5 per cent dextrose in saline solution or distilled water depending upon the case treated When the maximum effect is desired no diluent is used 200 to 600 c c can be used undiluted at a rate of flow of 4 to 5 c c per minute although twice that amount can be safely given There is no formula by which one can determine exactly the amount of plasma necessary to administer in a given case The safe and practical procedure is to give enough to restore and maintain the normal blood volume

Plasma can be given intravenously intramuscularly by hypodermoclysis and even subcutaneously as it is effectively absorbed from the extravascular spaces Some believe the rate of utilization is more effective if given by the intramuscular rather than the subcutaneous route No incompatibilities are encountered in its administration

Advantages of Plasma

Under certain circumstances plasma has advantages over the use of whole blood

A It is immediately available for use in emergencies
   a It keeps well at room temperature and does not have to be preserved in a refrigerator
   b It can be transported readily
   c It can be given without cross matching
   d Serologic examination is completed before the plasma is stored
B It can be stored for a much longer period than whole blood
C It can be given intramuscularly and subcutaneously the rate of absorption being approximately that of physiological salt solution

Indications for Plasma

Surgical

1 Primary and secondary shock The special value of plasma is that like whole blood it restores blood volume physiologically except for the red cells which may

have been lost through bleeding Plasma is far superior to salt solution glucose or acacia for treating shock
2 Dehydration
3 Burns
4 Wound healing and disruption
5 Increased intracranial pressure
6 Post operative pulmonary atelectasis and edema
7 Pre anesthetic preparation for the 'bad risk liver

Medical

1 Gastrointestinal Conditions
   A Nutritional edema and hypoproteinemia
      a Exogenous
      b Endogenous
   B Hemorrhagic States
      a *Hemorrhagic gastritis*
      b Bleeding gastric or duodenal ulcer
      c Ulcerative lesion of large intestine
   C Postoperative obstruction complicating gastric surgery
2 Nephritis and Nephrotic States
   A Anurias
3 Cardiac States
4 Infections
   A Bacillary dysentery
   B Peritonitis following a ruptured viscus
   C Measles
   D Scarlet Fever
   E Mumps
   F Pertussis
   G Poliomyelitis
   H *Viral pneumonias*

CONVALESCENT SERA

Alever (1) has recently reviewed the large amount of work done with convalescent sera by the Serum Centers which have been established in our large cities The experience of these Centers has demonstrated beyond doubt that convalescent serum is of therapeutic value *In their hands it has been most satisfactory in the prevention and treatment of measles scarlet fever and mumps*

The Use of Convalescent Sera in Measles

Both convalescent serum and pooled *normal adult* serum or plasma have been effective in the prevention of measles as well as in the treatment of the disease during the preeruptive stage

10 to 20 ml of convalescent serum depending upon the age of the exposed child is given intramuscularly within the first 7 days after exposure This has resulted in from 50 to 70 per cent complete protection and 20 to 40 per cent of modified measles

Recent work (2-6) indicates that the intravenous administration of large doses of serum also may be of some value in lessening the acute symptoms when treatment is begun after the eruption has appeared

The Use of Convalescent Sera in Scarlet Fever

Convalescent serum will reduce the incidence of scarlet fever among the exposed individuals from 10-15 per cent to only 1 per cent who show a typical course and 0 5 to 2 per cent who will have a mild or modified measles The serum is administered intramuscularly in dosage of 10-40 ml depending upon the age of the patient and within 24-48 hours after exposure A protective dose of the serum should be repeated every 10 days if exposure continues since this passive immunity only lasts for 10 days

Excellent results have been reported (1-5) in the treatment of scarlet fever by the intravenous use of serum which should be administered during the first 36 hours of the disease The dosage varies from 20 to *100 ml depending upon the age of the patient In* 75 to 85 per cent of the patients so treated the acute symptoms subside in 12 to 24 hours Complications are reduced by 50 per cent and those that develop are *mild in nature The dose should be repeated at 48* hour intervals if the disease does not clear

Scarlet fever convalescent serum has given good results in erysipelas pharyngitis cervical adenitis post-operative complications of mastoiditis and pneumonia

Convalescent serum used in conjunction with the sulfonamides has shown striking results and is due apparently to a synergistic effect of the combined therapy (2-9)

The Use of Convalescent Serum in Mumps

The development of mumps has been prevented in 90-95 per cent of exposed individuals by the intramuscular administration of 20-40 ml of convalescent serum given within one week after exposure Thalheimer (2) reports prompt subsidence of acute orchitis following the intravenous administration of 40 ml of convalescent serum The author has been unable to duplicate these results on several similar patients

The Use of Convalescent Serum in Whooping Cough

10 to 20 ml of pertussis convalescent serum administered intramuscularly to 215 infants and young children during the 1st week after exposure resulted in complete protection in 78 per cent mild illness in 10 per cent moderate illness in 6 per cent and typical whooping cough but without complications in the remaining 6 per cent (1) If the exposure is continuous *it is recommended* that the dosage be repeated every 5 to 7 days

Good results have been reported in the treatment of the acute disease by the intramuscular administration of 20 ml of serum repeated daily for 3 or 4 doses Subsidence of the major symptoms occurred within 10 to 14 days in about 69 per cent of cases with a death rate of only 1 5 per cent

The Philadelphia group now recommends that the intravenous route of administration be used in the treatment of acute disease and currently 60 to 100 ml of serum is being given intravenously to critically ill infants and repeated if necessary

Summary

These indications of the possible value of fresh plasma or serum in the treatment of acute infections are evidence that there may be various therapeutic properties of blood and blood derivatives as yet unexplored More investigation must be carried out to determine the value of convalescent serum in poliomyelitis (10-12) virus pneumonia (12 13) and other acute infections The evidence of the effectiveness of this therapeutic agent in the prevention and treatment of measles scarlet fever mumps and whooping cough is sufficiently important to warrant the interest of every state health officer as well as physician

BLOOD TRANSFUSION

The citrate method of blood transfusion is now in almost universal use Many excellent methods of collecting blood with closed systems have been devised While the open system method is the easiest it is the opinion of many that it is not the most reliable Being generally available however its technique and materials necessary for the procedure will be described

Materials Needed

1 Iodine and alcohol for skin preparation
2 Gauze sponges for filters and skin preparation
3 Pressure cuff for arm of donor
4 Novocaine to anesthetize the skin wheal of donor
5 Needles of #15 #16 #18 and #26 gauge
6 1000 c c graduate for collecting blood
7 Rubber tube 16 inches long with metal adapter for the needle (to collect blood)
8 Tourniquet or inflatable cuff for recipient s arm
9 50 c c ampoule of sodium citrate (2 5 per cent sol) for anticoagulant
10 4 ounce glass funnel for filtering blood
11 Flask tubing and Murphy drip for giving blood
12 Standard and hot water bottles
13 100 c c of saline (1 per cent) to start *the transfusion*
14 10 c c syringe for injection of novocaine

Technique

The donor lies recumbent on his back with one arm placed in a comfortable position upon an arm board A blood pressure cuff is placed upon the upper arm and the site for venipuncture is prepared with alcohol and iodine and draped with sterile towels The 50 c c ampoule of 2 5 per cent sodium citrate solution is broken and the contents are poured into the measuring flask The tubing and transfusion needle are irrigated with this solution to prevent clotting of the blood A small wheal of novocaine is raised over the proposed site of puncture The pressure of the blood pressure cuff is raised to about 70 mm of mercury pressure and is kept at this level during the collection of blood A No 15 gauge needle is usually used in drawing the blood

The distal end of the rubber tubing is placed in the measuring flask needle and adapter are connected to it and the needle introduced into the vein The donor is told to open and close his fist thus promoting the flow of blood The flask is gently shaken or rotated in order to mix the blood thoroughly with the citrate solution and prevent its clotting Usually 500 c c are withdrawn after which the needle is removed the cuff having been first deflated and a pressure dressing applied to the site of puncture The donor is permitted to lie quietly for a period of about 15 minutes and urged to drink freely of water or other fluids

If the blood is not filtered before it is given to the recipient it is possible for small clots to block the needle It is usually easier to precede the transfusion by the injection of a small amount of saline The use of saline prevents loss of blood during the removal of bubbles from the tubing and facilitates the insertion of the needle in the vein One hundred c c of physiological saline are poured into a flask the air is expelled from the tubing and a No 18 needle attached and introduced into the vein The transfusion is started with the saline but as soon as the saline is running the blood is added to the flask being filtered through a layer of gauze placed in the glass funnel

Blood Transfusion Reactions

A **Incompatible Reactions** Due to errors in typing, cross matching or undetermined factors

1 Deteriorated or weak typing seras
2 Failure to cross match
3 Disarranging tubes of donor's and recipient's cells and serums so that the wrong cells and serums are cross matched
4 Use of wrong donor
5 Use of the same donor for second or third transfusion without cross matching

B **Chill and Fever Reaction** Reactions occurring about 30 minutes after completion of the transfusion starting with a chill followed by a rise in temperature of from 2 to 4 degrees and subsiding in about 4 hours

1 *Pyrogens* Pyrogens are universally present in surface waters which are the source of most water supplies Pyrogens are by products of bacteria These products are not destroyed by sterilization and are not readily entrained and are carried over in the distillate Pyrogens have been shown to be the most frequent cause of transfusion reactions They may be present in the citrate solution in accessory glucose or saline solution or in the donor's or the recipient's set

2 *Contaminated Blood* Contamination may be very slight and the organisms of such low virulence that infection will not occur when the contaminated blood is transfused but the products of the growth of the bacteria may cause chills and fever

C **Allergic Reactions** These may result from the transfer of allergy from donor to recipient or of substances to which the recipient is sensitive Such reactions are easily controlled by adrenalin, minims 3 and are seldom important They can be avoided by using non allergic donors and by insisting on the use of fasting donors

D **Jaundice Reactions** With or without chill and fever and not due to the transfusion of incompatible blood

1 Blood stored beyond its safe storage period increased fragility of stored red cells resulting in their being destroyed in the blood stream of the recipient
2 Contaminated stored blood increasing the fragility of the red blood cells so that sufficient hemoglobin is released to cause jaundice

Prevention of Reactions

Now that blood banks have been established in most large hospitals, many transfusions are given in a more or less routine manner Whole blood should only be given where it is urgently needed, and not simply as a "boost" or because of its availability When whole blood is to be given the following measures must be observed

1 Both the patient and the donor must be typed with high titer serums

2 Banked donor blood should be re typed before use, even though it has already been labeled

3 The donor's cells should be cross matched with the recipient's serum using the Landsteiner Levine test tube technique The slide cross matching technique is often unreliable

4 The results of the cross match should be checked by an experienced technician or by an experienced physician To rely on inexperienced personnel may result in tragedy

5 Whole blood should never be given to a patient while under the influence of a general or a spinal anesthetic

6 If the patient is pregnant or has been delivered or if more than one transfusion is contemplated, a Rh determination should be performed

During the administration of the first 50–100 c c the patient should be carefully watched by an experienced observer, and the transfusion should be immediately discontinued in the presence of a reaction however slight The great danger is renal blockage, due to a *deposition of hematin in the kidneys* This is much more apt to occur if the kidneys are excreting acid urine Consequently if there is any likelihood of a reaction the urine should be rendered alkaline before beginning the transfusion by giving sodium bicarbonate or sodium lactate

BLOOD GROUPING TECHNIQUE

Two drops of blood are placed in a 5 c c test tube half full of physiological saline solution The tube is twirled to secure uniform mixing Two rings are drawn with a wax crayon about 2 cm in diameter on a glass slide and marked one A and one B Two drops of type A serum are placed in the circle marked A and 2 drops of type B serum in the circle marked B One drop of the suspension of blood cells is added

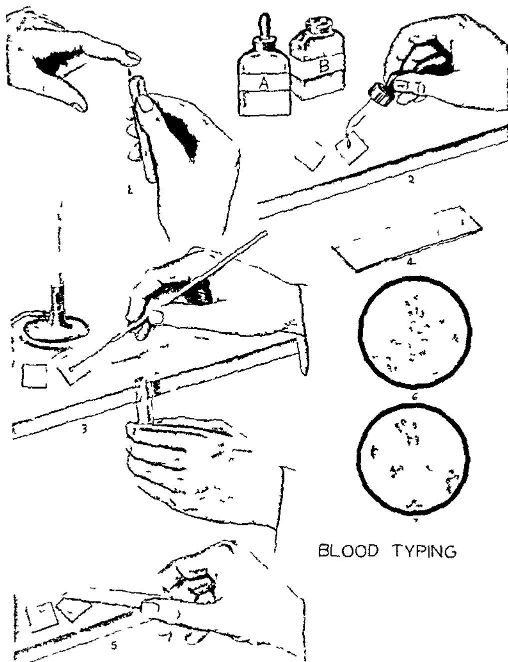


Fig 232 Blood Typing

1 Add drop of unkno n blood to 20 drops of normal saline
2 Place a drop of serum A on a cover gla s and a drop of serum B on another cover glass
3 Add a drop of diluted unknown blood to each cover glass flaming the loop between drops
4 Place two mall rings of petrolatum on a glass slide
5 Place glass slide face down over the cover lips sealing the drop in
6 No agglutination
7 Agglutination present

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Procedure

1 Fold large sheet diagonally into folds five inches wide and fold ends toward the center
2 Turn top covers back in form of a triangle remove pillows and place restraint under shoulders
3 Bring each end under axilla up over shoulders cross ends underneath restraint at back, and tie securely to upright rods where they join the horizontal rod at the head of the bed
4 Place soft pillow under head to prevent head from resting on restraint

Body Restraint

Articles Needed

Large cotton sheet
Basin of water
Whisk broom

Procedure

1 Fold large sheet lengthwise in three
2 Place folded sheet over patient s body extending from axilla below hips
3 Dip whisk broom in basin of water and dampen the ends of the sheet
4 Roll ends of sheet around rods at sides of of the bed and be sure they are secure

Note If applying to women with large pendulous breasts place soft rings around each breast

Jacket Restraint for Children

Articles Needed Restraining jacket

Procedure

1 Slip arms through the jacket and button the jacket in back
2 Tie shoulder straps to the head of the bed
3 Pass side straps under bed cross them and tie to rod on each side of the bed

To Restrain Child for Examination of Ears Nose or Throat

Articles Needed Draw sheet

Procedure

1 Fold draw sheet diagonally
2 Place under child s body with double edge close to neck
3 Bring point up over child's feet place arms at side and bring sides of sheet around body thus holding arms securely
4 The nurse then places child s feet between her knees place left arm around body and use right hand for holding head

Elbow Restraint

Articles Needed Two elbow restraints

Procedure

1 Fold surplus muslin under upper edge extend child s arm and tie around elbow thus preventing child from bending arms and scratching face or removing dressing

LIFTING AND TURNING PATIENTS

Position in Lifting Place the knees or thighs against the side of the bed take deep inspiration hold the abdominal muscles taut and in lifting allow the weight to come on the muscles of the chest and shoulders

To Lift a Patient Up in Bed

1 Remove the pillows
2 Instruct the patient to flex his knees and press the heels against the mattress
3 Place one arm under the patient s shoulders to opposite axilla and the other hand under the knees
4 Instruct the patient to lift his hips and help move up in bed at the same moment the nurse lifts him

To Lift a Very Heavy or Helpless Patient In case of injury or after operation when moving may endanger the patient two nurses will be required to lift the patient The nurses stand on the same side of the bed One nurse places her arm under the patient s shoulders and the other under his hips The second nurse places one arm under the patient s back and the other under his knees The lifting is done simultaneously This may be done with one nurse on either side of the bed—place hands and work together

To Help a Patient into Bed The patient is assisted onto a foot stool he then sits on the side of the bed The nurse supports the patient s shoulders with one arm and places the other arm under the knees and turns the patient into bed

to the serum in each of the circles The slide is tilted back and forth or the cells and serum are mixed with a toothpick and the slide covered with a cardboard slide box to prevent evaporation Examination is made in 20 minutes under the microscope (high power)

No agglutination = Universal donor (O)
Agglutination in (A) = Type (B)
Agglutination in (B) = Type (A)
Both agglutinated = Universal recipient (AB)

CROSS MATCHING

Serum is obtained from patient and donor by bleeding from arm vein into a centrifuge tube allowing the blood to clot and separating the serum by centrifugation Tests of donor s cells are set up with recipient s serum and of recipient s cells with donor's serum as described above for grouping Mixing should be thorough and a final reading on the cross matching should not be given before 20 minutes

The significant side of the reaction is between the donor s cells and the recipient s serum if agglutination occurs when these are mixed the blood cannot be used Typing alone is not adequate protection against the hazards of transfusion reactions Blood from a universal donor can usually be given with safety to patients of any blood group While patients who are universal recipients can theoretically receive blood from donors of any group and type to type transfusions should be quite safe *it is not wise except in cases of urgency to give blood which has not been cross matched*

If a transfusion of blood is given in which the recipient s serum agglutinates the donor s cells a serious fatal reaction may occur when the clumped cells reach the pulmonary capillaries and cause multiple small emboli

The minor reaction between the recipient s cells and the donor s serum is of little consequence and can be overlooked There is no advantage in type to type transfusion as compared to the use of blood from a universal donor which agglutinates on the minor side

RESTRAINTS

Varieties

1 Cribs
2 Side boards
3 Sheets
4 Wrist or ankle restraints
5 Elbow restraints
6 Body restraints
7 Jacket restraint for children

Wrist Restraint

Articles Needed Two wrist restraints

Procedure

1 Roll each end of wrist restraint to within 18 inches of padded portion and pin securely
2 Fold back covers in form of a triangle place arm in comfortable position extended *and not too near the edge of the bed*
3 Make clove hitch knot on outer side of wrist and single knot on outer side
4 Test by slipping two fingers under restraint to see that it is not too tight
5 Twist ends tightly make a single knot and tie around rod at side of the bed with a double knot
6 Unpin ends fasten short end to the head of the bed and the long end to the foot of the bed Tuck the surplus under the mattress

Ankle Restraint

Articles Needed

1 Ankle restraint
2 Four safety pins and four common pins

Procedure

1 Turn back covers neatly at foot of bed
2 Straighten lower limbs
3 Place center of the restraint over ankles cross ends underneath draw up between ankles and tie in a double knot
4 Twist the ends make a single knot tie to upper rod at foot of bed and twist the ends down the upright rod
5 Tie to center of horizontal rod with double knot and tuck surplus under mattress
6 Place covers over foot of the bed and pin to springs at sides with safety pins Fold over surplus and pin in place with common pins

Shoulder Restraint

Articles Needed Large cotton sheet

5 Place binder under the patient
6 Cover area to which poultice is to be applied with a thin flannel
7 Test temperature on arm and apply poultice slowly
8 Cover with protector and hold all in place with bandage binder
9 Change every 1 or 2 hours
Note Add dissolved mustard (1–6) to poultice for mustard poultice

To Discontinue Poultice

1 Remove poultice and dry the part.
2 Powder lightly and cover part with flannel for two or three hours

Mustard Paste

Articles Needed

1 Mustard and flour
2 Small bowl and spoon
3 Poultice board
4 Old muslin
5 Towel and stupe cover
6 Olive oil and swab
7 Bandage or binder
8 Powder
9 Tepid water and pitcher

Procedure

1 Spread towel on poultice board then stupe cover and muslin of desired size
2 Measure mustard and flour and thoroughly mix using one part mustard to four parts of flour (for children use 1 to 6)
3 Add water sufficient to make paste White of egg may be added to prevent blistering
4 Spread paste about half an inch thick on muslin and fold envelope fashion
5 Roll in towel and carry it to bedside
6 Oil the skin with olive oil apply paste and cover with stupe cover
7 Hold in place with binder
8 Remove when skin is sufficiently reddened
9 Dry moisture on skin by patting
10 Powder lightly and cover with piece of soft muslin

Croup Tent

Articles Necessary

1 Wooden frame
2 Croup tent blanket
3 Linen covering
4 Electric hot plate
5 Croup kettle

Procedure

1 Place wooden frame around the head of the bed
2 Cover with croup tent cover Leave side near bedside table open
3 Place linen covering on in same manner
4 Connect electric hot plate put water and medication in croup kettle and place on hot plate Have spout of kettle extend into opening at side

COLD SPONGE BATH

An attempt to lower an excessively high body temperature by increasing the heat loss from the body Indicated whenever hyperpyrexia is present and especially when symptoms of delirium occur

Articles Needed

1 Bowl containing 6 gauze compresses on ice
2 Basin with tepid water
3 Basin of water 60–70 F
4 Bath blanket
5 Long rubber sheet
6 Two cotton sheets
7 Ice cap and cover
8 Hot water bottle and cover
9 Foot tub
10 Alcohol 50 per cent for back wash

Procedure

1 Collect equipment make a lengthwise roll of blanket rubber and cotton sheet
2 Carry equipment to bedside and explain treatment to patient
3 Screen patient—cover him with cotton sheet at the same time fanning the bed clothing at the foot of the bed
4 Remove both pillows unless contraindicated and remove patient s gown
5 Place lengthwise roll under patient so that the rubber will protect the blanket

To Arrange a Patient Comfortably on His Side in Bed

1 Put rubber pillow case on feather pillow Turn the patient on his side, flatten one edge of a feather pillow and place well under his back Roll opposite edge under itself for additional support
2 Turn the patient on pillow by grasping the shoulder with one hand and the hips with the other
3 Flex the knees the upper limb more than the lower Place a small pillow covered with a rubber pillow case between the knees as this helps to relax the abdominal muscles

To Draw Up Mattress with Patient in Bed Remove pillows The nurse stands at the head of the bed and grasps the mattress at each side The patient may assist by grasping the rod at the head of the bed with both hands and drawing himself up The knees are not flexed Extend the legs on the bed If two people pull up the mattress one stands at either side at the top of the bed Each person grasps the mattress with two hands—one hand at the side of the mattress and the other hand in the middle at its top The signal is given and both pull together

To Place a Patient in a Wheel Chair Dress patient with underwear stockings slippers wrapper and bathrobe Place the wheel chair at the foot of the bed and arrange a double blanket crosswise over the seat of the chair Raise the patient to a sitting position support the back with one arm place the other arm under the knees and draw the patient s limbs over the edge of the bed Stand in front of the patient place hands under each axilla and assist him on to the chair Fold the blanket snugly about the patient s body and pin with safety pins Tuck the blanket securely under the feet Fold the single blanket lengthwise place about patient s shoulders and fold back the edge to form a collar Pin about the wrist

COUNTERIRRITANTS

Abdominal Turpentine Stupes

Articles Needed

1 Two pieces of flannel
2 Towel and protector
3 Basin of hot water
4 Turpentine and oil (1 4)
5 Swab for applying turpentine and oil
6 Stupe wringer
7 Electric hot plate
8 Alcohol and powder
9 Blanket

Procedure

1 Protect chest and abdomen with blanket, turning down covers to edge of the blanket
2 Protect bed covers with a towel
3 Apply turpentine and oil to abdomen with a s ab
4 Wring flannel out of hot water in stupe wringer
5 Shake flannel quickly to incorporate air, arrange in loose folds and cover with stupe protector
6 Have fresh stupe ready before removing the old one and never allow the stupe to become cold
7 Change every 2 to 4 minutes
8 Apply turpentine and oil every fourth time

To Discontinue Stupes

1 Remove oil and turpentine with alcohol
2 Powder lightly and cover part with flannel

Flaxseed Poultice

Articles Necessary

1 Flaxseed meal
2 Saucepan and boiling water
3 Large spoon
4 Poultice board
5 Old muslin and piece of thin flannel
6 Bandage or binder
7 Towel and protector

Procedure

1 To one and one half cups of boiling water gradually add one cup of flaxseed meal Stir mixture thoroughly
2 Boil two minutes or until mixture drops readily from the spoon Beat well to incorporate air
3 Spread one half inch thick on old muslin and fold envelope fashion
4 Carry to bedside wrapped in poultice cover and towel

5 Place binder under the patient
6 Cover area to which poultice is to be applied with a thin flannel
7 Test temperature on arm and apply poultice slowly
8 Cover with protector and hold all in place with bandage binder
9 Change every 1 or 2 hours
Note Add dissolved mustard (1-6) to poultice for mustard poultice

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3 Basin of water 60-70°F
4 Bath blanket
5 Long rubber sheet
6 Two cotton sheets
7 Ice cap and cover
8 Hot water bottle and cover
9 Foot tub
10 Alcohol 50 per cent for back wash

Procedure

1 Collect equipment make a lengthwise roll of blanket rubber and cotton sheet
2 Carry equipment to bedside and explain treatment to patient
3 Screen patient—cover him with cotton sheet at the same time fanning the bed clothing at the foot of the bed
4 Remove both pillows unless contraindicated and remove patient s gown
5 Place lengthwise roll under patient so that the rubber will protect the blanket

and mattress and the patient will be protected *from the rubber by the sheet* (*If* turning of patient is inadvisable, the bed may be protected by the draw sheet *folded in quarters placed under each* part as it is bathed)

6 Place hot water bottle protected with *cover at patient's feet*

7 Bathe the face with tepid water using patient's washcloth Dry the towel and *apply ice cap to head*

8 Apply cold compresses to axilla, back of neck, abdomen, and groin Change *compresses as often as necessary* to keep them cold

9 Sponge parts in the following order
 a Arm on farther side
 b Arm on nearer side
 c Chest
 d Thigh on farther side
 e Lower part of leg on farther side
 f Thigh on nearer side
 g Lower part of leg on nearer side
 h Back

 Rub back with alcohol Leaving the back until last makes it possible to complete the treatment turning the patient only once

10 Application is made in the following manner
 a Apply vigorous friction with rotary motion to each part exclusive of the abdomen sufficient to produce a feeling of warmth in the skin
 b Application of tepid water followed immediately by one of cold water is to be made by cupping one hand and taking up a small amount of water in it Continue to apply friction to the part with the other hand
 c Proceed rapidly from one part to the next being careful to pat dry and cover each part before proceeding to the next

 WATCH PATIENT'S COLOR PULSE AND RESPIRATION CLOSELY

11 When sponge is completed remove the rubber and cotton sheets and place the blanket around the patient protecting adjacent skin surfaces

12 Bring up top covers at the same time *removing the sheet which covers the* patient

13 Refill ice cap and hot water bottle if necessary

14 Remove the articles used for the treatment from the bedside

15 *One Half Hour* after sponge remove ice cap and hot water bottle put on patient's gown remove the blanket and take rectal temperature If patient is sleeping this may be delayed

Alcohol Sponge Proceed as for cold sponge using 50 per cent alcohol instead of cold water

COLD PACK

Articles Needed

1 Two bath blankets
2 One long rubber sheet
3 Three cotton sheets
4 One bath towel
5 Ice cap with cover
6 Hot water bottle and cover
7 Bath thermometer
8 Hot fluids and feeding cup
9 Foot tub containing water—temperature 70° to 80° F
10 Alcohol and powder

Procedure

1 Roll rubber sheet between cotton sheet and bath blanket
2 Fan bath blanket crosswise
3 Fan one cotton sheet lengthwise and one crosswise and place in a foot tub
4 Carry equipment to bedside
5 Place blanket over chest Tuck well in around shoulders and fan clothing to the foot of the bed
6 Adjust bath towel over loins and remove gown
7 Place roll made of blanket rubber sheet and cotton sheet under patient with blanket next to the bed
8 Wring out sheets from water of required temperature
9 Place the sheet folded lengthwise under patient *bring up and tuck well around* the patient

10 Wring out second sheet place across chest make secure at neck and shoulders bring down over patient and tuck well around patient
11 Bring up top covers and leave in pack from 20 minutes to 1 hour

To Remove from Pack

1 Fold down covers to foot of the bed
2 Remove blanket and upper sheet then under wet sheet and rubber heet
3 Dry patient with towel wrap lower blanket around patient
4 Bring up bed clothing and leave for twenty minutes
5 Give hot milk or broth and friction if patient is chilly
6 At end of twenty minutes remove blankets *rub with alcohol and put on gown*
7 Take temperature pulse and respiration and record

HOT PACK

Articles Necessary

1 Seven blankets
2 Two long rubber sheets
3 Ice cap and cover
4 Rubber pillow case
5 Towel
6 Stupe wringer and two stupe sticks
7 Feeding cup and two stupe sticks
8 Alcohol and powder

Procedure

1 Roll blanket lengthwise rubber sheet between three blankets (thin blanket on top to wrap around patient)
2 Fan one isolation blanket crosswise
3 Fan rubber sheet and blanket crosswise
4 Fan two isolation blankets lengthwise
5 Carry articles to bedside Screen patient
6 Cover patient with blanket at same time fanning down covers to foot of bed
7 Remove gown
8 Turn patient on side Place roll of blankets and rubber sheet under patient
9 Tuck sides of under blanket under sides of mattress
10 Bring up sides of thin blankets which is under patient and tuck well in around arms and legs, so that no skin surfaces touch
11 Fan blanket which covers patient to foot of bed
12 Apply ice cap to head
13 Wring dry blankets in sterilizer bring to bedside of patient in stupe wringer in a foot tub
14 Turn patient on side and after shaking blanket quickly, place under patient and tuck well around arms and legs
15 Shake second blanket and place over patient tuck well around body
16 Bring up dry blanket at foot of bed and tuck in around patient
17 Bring up blanket and rubber sheet on each side
18 Place second rubber sheet and blanket over all and tuck in at side
19 Place folded towel over blankets where they come in contact with patient s face
20 Draw up upper bed clothing and leave in pack 20 to 30 minutes as ordered
21 Give fluids while in pack
22 Avoid drafts and note pulse frequently

To Remove From Pack

1 Fold outer clothing to foot of bed
2 Remove top rubber sheet and wet blankets
3 Remove under wet blankets and rubber sheet leaving patient between blankets for one hour
4 At end of one hour rub patient with hot towels give a hot alcohol rub and put on *gown*
5 Remove blankets

EAR EYE NOSE AND THROAT IRRIGATIONS

Ear Irrigation

Articles Needed—Tray containing

1 Sterile basin with irrigation solutions
2 Syringe in disinfection solution
3 Sterile cotton applicators
4 Kidney basin
5 Towel
6 Waste cup

Procedure

1 Have patient sitting up if possible
2 Protect shoulder with towel and have patient hold kidney basin close to ear

3 If a discharge is present, wipe out with applicator
4 Draw the fluid into the syringe, hold up right and expel the air For the adult draw tip of ear upward and backward to straighten the canal For children draw tip downward and backward
5 Inject fluid slowly into the auditory canal, being careful not to place point of syringe too far into the ear
6 Wipe out carefully with sterile applicator
7 Leave the tray in order

Note If irrigating can is used it should be placed not more than three or four inches above the level of the patient's ear A glass connecting point is attached to rubber tubing and used for injection of fluid into the ear

Nasal Irrigation

Articles Needed

1 Irrigating standard
2 Tray containing
   a Irrigating can with tubing clamp and solution
   b Nasal douche point
   c Emesis basin
   d Dressing rubber and towel

Procedure

1 Have patient sitting up if possible
2 Cover dressing rubber with towel and place across the patient's chest
3 Hang irrigating can on standard three or four inches above patient's head
4 Keep patient s head tilted forward so that Eustachian tubes are higher than the nose
5 Have the patient hold the emesis basin in position
6 Instruct patient to breath through mouth
7 Irrigate one nostril then the other using two or three ounces at a time One pint is sufficient for irrigation
8 Leave tray in order

Note If one nostril is obstructed solution should be injected into that nostril first

Throat Irrigation

Articles Needed

1 Irrigating standard
2 Tray containing
   a Irrigating can with tubing clamp solution
   b Drinking tube
   c Dressing rubber and towel
   d Basin

Procedure

1 Patient can either be sitting or in recumbent position, head bent forward
2 Place dressing rubber covered with towel in such a way that it will protect the patient and the bed
3 Place irrigating standard so that can is two feet above patient's head
4 Put basin in place to catch solution
5 Connect glass drinking tube to rubber tubing
6 Move glass tube from side to side so that the solution will reach all parts of the pharynx
7 Remove articles and boil the tube

Eye Irrigation

Articles Needed

1 Bowl or bottle of solution for irrigation
2 Sterile eye dropper fitted with rubber bulb
3 Jar of sterile cotton pledgets
4 Sterile thumb forceps
5 Kidney basin or cellulose cotton
6 Waste cup or paper bag
7 Towel
8 Dressing rubber if necessary

Procedure

1 Have patient sitting up in chair with head bent back if possible
2 Wipe eye carefully with cotton pledget from inner to outer canthus
3 Have patient hold the kidney basin close against cheek
4 Hold lids open with left hand and irrigate with right hand
5 Dry the eye with cotton pledget
6 Leave tray in order

Note If patient is too ill to sit up remove pillows cover dressing rubber with towel and place so as to protect the patient s chest and bed Place kidney basin under side of head and proceed in the same way

Ear Irrigations for Babies

Articles Needed

1 Irrigating can and tubing solution
2 Clamps and emesis basin

3 Restraining sheet and rubber bib
4 Kelly pad
5 *Dressing pail*
6 Return flow ear tip (Luca's)
7 Cotton wipes and swabs
8 Irrigating standard

Procedure Place can with fluid not more than 12 inches above child s head Temperature of fluid if for cleansing 100 to 105 degrees if to relieve inflammation 110 degrees Turn down clothing around neck restrain adjust bib wipe out any discharge of outer ear Lay baby with head on covered rim of the Kelly pad place pus basin so as to receive return flow Allow a little fluid to run through tip until warm Insert snugly in the ear Pull downwards and backwards on the lobe of the ear to straighten out the canal if the child is under two years of age For children over two years of age pull upwards and backwards Syringe until the return flow is clear

Nasal Irrigations for Babies

Articles Needed Same as for ear irrigation except that a small hard rubber tip is used instead of an ear tip

Procedure Place the irrigating can of fluid not more than two inches above the child s head Restrain the child as above Place child with his head on the covered rim of the Kelly pad Allow a little fluid to run until warm Have the nostril to be irrigated uppermost Insert tip in upper nostril Return flow should come back through the lower nostril If necessary turn the child over and irrigate the other nostril

Throat Irrigations for Babies

Articles Required and Procedure Same as for nasal irritation except that a long hard rubber tip is placed in the upper angle of the mouth well back but not touching the back of the throat The fluid should flow across the throat and out the lower angle of the mouth If the child is inclined to swallow the fluid hold with his chin pressed down on his chest while irrigating or sometimes turning on his stomach and holding his head over the edge of the basin or the Kelly pad will prevent his swallowing the fluid

Eye Drops

General Principles Clean the hands and avoid touching the eye with the dropper Use the dropper only once unless it has been boiled Solution temperature 70 to 98°F Dosage is usually one to two drops Patient looks upward lower lid held with index finger the hand steadied against the malar bone Medication is dropped at the center of the lower conjunctival sac Close eyelid slowly to spread drops catching overflow with a sterile gauze or cotton ball Press on inner canthus to prevent drops entering the nose when using poisonous drugs such as atropine or cocaine

Eye Ointments

Eyelids Cleans lid margins with soap and warm water Squeeze a little ointment onto index finger and massage eyelid gently

Eye Pull down lower lid as for drops and then squeeze a little ointment into the lower conjunctival sac close eye allow ointment to spread over conjunctiva

Eye Powder Dust powder from sterile applicator lightly into eye close lid gently and allow powder to dissolve in moisture in conjunctival sac

Hot Eye Compresses

Explain the procedure to the patient Wash hands before and after procedure It is well to consider any discharge from the eye infectious Remove discharges before applying compress Use clean smooth compresses do not extend compresses over nose or eyebrow discard after one using Apply firmly but avoid pressure on the eyeball Do not use forceps too near the eye Do not apply heat longer than 20 minutes as continuous heat causes waterlogging and destruction of tissues Follow hot applications with medications ordered In using electric appliances examine cord and connections carefully for short circuits Do not burn patient

Solutions Boric acid 2 to 4% physiological saline solution

Materials Olive oil or sterile white petrolatum in tube solution bowl and solution 6 or more 2 x 1½ inch oval pads cotton pledgets 2 strips ¼ inch adhesive 5 inch medicine dropper 2 forceps paper bag safety pin face towel

Cold Eye Compresses

Scrub hands before and after treatment If discharge present use compress only once Use firm but gentle touch Avoid pressure on

the eyeballs Treatments last not longer than 20 minutes—1 hour apart Have a tray covered with a clean towel, 6 or more 2 x 1½ inch oval pads dressings, bowl for ice (cover ice with gauze) face towel, cotton balls solution, paper bag safety pins kidney basin if there is no discharge

Explain treatment to the patient Have him move to the edge of the bed and lie in dorsal recumbent position Remove all pillows but one unless patient has difficulty in breathing Attach paper bag to bedside with safety pin Place towel across chest and with clean cotton moistened in solution remove any eye discharge Fold compress once moisten with solution place on ice, when thoroughly chilled, place on eye Change them every ½ minute, oftener if patient has very high temperature Dry eye and face and record patient's reactions to treatment as well as the condition of the eye

THE USE OF PHOTOGRAPHS IN CASE STUDY OF PATIENTS

Photographs taken at intervals throughout the period of treatment are obviously highly desirable records of the growth general physical changes and the stature of the patient If photographs are made they should be taken against a background marked in such a way as to make comparisons with a series of subsequent photographs practical

Squared backgrounds may be used and it would seem that white lines on a black background offer the greatest contrast to white nude figures This scheme can be reversed for colored nude figures

Conditions must be uniform as to lighting and distance of focus on all photographs In this connection it can be stated that photoflood bulbs are inexpensive and highly satisfactory

Close ups of areas of particular interest especially when made for purposes of comparison should be taken at the same distance from the camera and should be accompanied by a scale

Anterior posterior and lateral (right and left) views of the nude patient should be taken and in all cases should be clearly labeled

DIAGNOSTIC PROCEDURES OF VALUE IN GENITO URINARY DISEASES

Urinalysis—Method of Collection

The word "voided' or "catheterized' should be recorded on the urinalysis report Without such a notation, one cannot attach much significance to finding pus in female urine In order to obtain a specimen of female urine as free as possible from contamination without resorting to catheterization, the patient should void two specimens discarding the first The second is kept for examination Having the patient wash the external genitalia before voiding gives further assurance of securing an uncontaminated specimen In the collection of male urines when urethritis or prostatitis is suspected or is to be excluded, two or three glass urine tests should always be used

In these multiple glass tests the patient voids into two or three glasses as the case may be without interrupting the urinary stream The first glass voided in either test, represents the bladder urine in addition to any material washed from the urethra In both the two and three glass tests when pus is found in the first glass only it may be assumed that the infection is confined to the anterior urethra A clear second glass specimen in either case means that the bladder urine is clear At the end of voiding there is a contraction of the bulbocavernosus and sphincter muscles which may squeeze pus from the posterior urethra seminal vesicles or prostate Herein lies the advantage of the three glass over the two glass test for if the second glass in the former test is contaminated with pus one cannot be sure that it does not come from the posterior urethra while in the three glass test the posterior urethral inflammation will contaminate only the third glass the second glass then representing only the bladder urine Therefore in the *two glass test* the first glass represents the anterior urethra and the second glass the bladder and posterior urethra In the *three glass test* the first glass represents the anterior urethra the second glass the bladder and the third glass the posterior urethra

Urine Cultures

These should be taken routinely in cases of pyuria Voided urine specimens are satisfac

tory for urine cultures in men The prepuce should be first retracted and the glans cleansed with alcohol, and while the patient is voiding a sterile test tube is held in the urinary stream until from 5 to 10 c c of urine are obtained In women, specimens must be obtained by catheterization *A man should not be catheterized merely to obtain a specimen of urine for culture*

Residual Urine Determination

This is determined simply by having the patient empty his bladder as fully as possible by voiding and then catheterizing The urine then obtained by catheterization is residual This is an important determination in bladder neck obstruction and bladder atonia it is an index of bladder decompensation

Prostatic Fluid Cultures

These are collected by cleaning the glans as for urine culture and having an assistant or the patient hold the sterile test tube under but not touching the meatus while the examiner massages the prostate Several drops of fluid are sufficient for culture

Rectal Examination and Examination of the Prostate Gland

If the patient s condition will permit, have him bend over the examining table The *tone* of the anal sphincter is noted by the lubricated gloved finger which is inserted into the rectum Atony may be evidence of central nervous system disease which may be the cau e of vesical symptoms believed due to obstruction The prostate gland is examined for *si e consistency contour* and *tenderness* The normal gland is flat movable heart shaped mildly sensitive and the palpating finger will encounter a notch in its upper border and a barely perceptible groove down the center separating the lateral lobes Usually the tip of the index finger is almo t as wide as either lobe The gland may enlarge in several planes either laterally longitudinally or it may increase in thickness so that it bulges back into the rectum more than the normal prostate The median commisure may be obliterated and the gland may enlarge in any combination of the planes mentioned The hypertrophied or infected prostate is either softer or firmer than normal in most cases The chronically infected prostate is frequently doughy in consistency The inflamed gland may show areas of hardness mixed with areas of softening The stony hardness of the carcinomatous prostate is characteristic when advanced though early cases may show only small areas of such induration and leave the examiner in doubt as to the diagnosis If routine rectal examinations were done by more physicians and not just by 'specialists,' more early carcinomas would be discovered especially in older men and consequently more cures by radical prostatectomy would be obtained The evaluation of size and

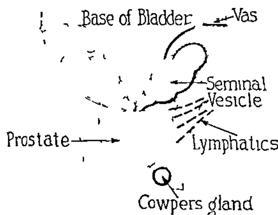


FIG 233 Prostate gland and adnexa in relation to rectal palpation The parts shown in heavy solid lines are only palpable when diseased

tenderness of the gland can be conveniently recorded using gradations from 1 to 4

Anal lesions are a frequent cause of pain in insertion of the rectal finger This pain should not be confused with that caused by pressure on an inflamed prostate gland The seminal vesicles can be felt when distended as cystic feeling pouches protruding upward from the upper portion of the prostate When inflamed they may be felt as hard cords

Examination of the Prostatic Fluid

Most prostatic fluid obtained following massage also contains ome eminal fluid constituents Since the seminal vesicles and the prostate are rarely if ever involved in an inflammatory process independently, there is little

need in attempting to differentiate between the two Various methods of massage have been described, but it appears to make little difference in the results which portion of the gland is stroked first and in what direction the strokes are carried out provided that the entire gland is massaged gently, using the ball of the finger and not digging the finger tip into the gland A final stripping motion down the mid portion of the gland and the posterior uretha will facilitate the obtaining of a specimen of fluid for examination By raising the peno-scrotal junction upward the slight obstruction caused by the suspensory ligament is relieved and the fluid may appear if not, the urethra should be stripped down beginning in the perineum over the membranous urethra and working down If the examiner is still unable to obtain a specimen, the patient should void a few c c of urine into a small container in which case the urine will be opalescent from the prostatic fluid present

The *normal prostatic fluid* is a thin opalescent fluid containing minute translucent lecithin bodies a few leucocytes and epithelial cells and sometimes a few corpora amylacea More than 5 or 6 leucocytes per high power field is considered abnormal Absence of lecithin bodies usually indicates obstruction of the prostatic ducts and inflammation Their reappearance after treatment is an index of improvement The amount of pus present in the specimen may be recorded in number of pus cells per low or high power field or the amount of pus as compared with the amount of lecithin bodies may be roughly estimated and the result expressed in per cent of pus present in the fluid It should be emphasized that one normal prostatic fluid does not preclude the existence of a prostatitis The first specimen is frequently negative Consequently more than one examination should be done if there is any reason to suspect prostatitis in spite of a negative specimen of fluid See Figs 229–231

Contraindications to Prostatic Massage The contraindications to prostatic massage are fairly well established

1 Tuberculous and carcinomatous prostates should never be massaged
2 No prostate containing a nodule should be massaged until it is definitely established that such nodule is neither tuberculous nor carcinomatous in origin
3 No gonorrheal prostate should be massaged until at least several weeks after the onset of the posterior infection, and even then, such massage should be confined to gentle pressure on the gland for the first three treatments
4 The prostate should not be massaged during the acute stage of any eye, heart, or joint lesion When it is instituted in the subsiding stages it should be repeated within three days of the subsidence of any distant reaction it has caused and it should be discontinued in any patient who is growing worse as a result of such massage
5 Diagnostic massage in the presence of any eye lesion should be of the gentlest sort If the eye lesion has any connection with the prostate gland very slight pressure on the gland will cause an increase in the eve symptoms

Massage of Cowper s Gland

This gland occasionally holds a chronic infection and should be kept in mind in those patients who have a scanty urethral discharge after the prostate has been rendered free of pus The forefinger is placed in the rectum and carried just to the side of the apex of the prostate With the thumb on the perineum to one side of the bulb, the inflamed gland or the induration around it can be readily massaged by kneading the tissues lying between the thumb and forefinger See figure 234

Massage should be undertaken twice a week If there is no result the gland may be excised

Method of Passing a Sound

Prepare the patient as for catheterization The right handed operator stands on the left side of the patient and introduces a well lubricated sound through the pendulous portion of the urethra while the penis is held parallel and close to the left inguinal canal The handle of the sound is then brought over toward the midline of the abdomen, meanwhile lifting the handle so that the shaft of the sound approaches and then passes the vertical plane As the sound passes into the membranous and then the posterior urethra and finally into the bladder the handle of the sound is carried downward toward the patient s thighs and

when the sound has been completely introduced the handle is usually between the thighs See figure 228 The sound will pass almost by its own weight through the normal urethra The vesical sphincter usually offers sounds smaller than 20 French in size is somewhat dangerous because the small sounds are likely to perforate the urethra For dilating strictures less than 20 French in size, filiforms and followers are used

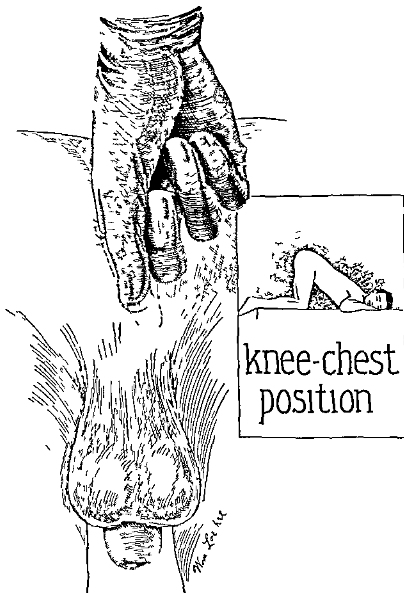


FIG 234 Examination and Massage of Cowper s Glands

a little resistance at first but this is overcome by gentle but continuous pressure Passing a sound consists chiefly in guiding a sound along the course that it naturally takes If the sound chosen will not pass without difficulty a smaller sound should be used The use of

Use of the Bougie and Acorn Sound

These are used for the diagnosis of strictured areas in the urethra

1 Cleanse the urethra with an antiseptic solution

2 Choose an instrument, the size of which

will pass through the meatus Pass it gently into the urethra until it meets an obstruction

3 *If it will not pass through*, remove and try smaller sizes until one passes through This tells the size of appropriate sounds needed *for dilatation*

4 The use of these instruments is confined solely *to the anterior urethra*

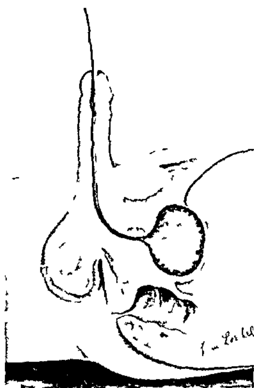


Fig 235 Use of the Bougie a Boule and Acorn Sound

Catheterization

In any case in which the usual measures and devices to induce voiding have failed catheterization becomes necessary The measures alluded to consist of allowing the patient to sit in a tub of warm water and void while in the tub to have him stand beside his bed if the patient is a male giving analgesics for pain is helpful enemas or the instillation of novocaine into the rectum sometimes succeeds Complete privacy and the sound of running water are definite aids in inducing voiding If catheterization is inevitable it should be done early in order to avoid over distension of the bladder for overdistension greatly weakens the resistance of the bladder to infection

Technique With the patient lying on his back and the genitalia exposed place a sterile towel across his thighs Clean the penis with alcohol or soap and water taking care to clean within the lips of the meatus Hold the cleaned penis up by its base and slip the sterile towel under with the other hand Discard the first part of the lubricating jelly as contaminated, and place the next portion squeezed from the tube on the towel Place a sterile catheter of suitable size upon the towel Size 14 or 16 catheter is suitable for routine catheterization, larger ones cause unnecessary trauma Wash the hands and by means of a sterile clamp and sterile gloves introduce the well lubricated catheter into the urethra, using one hand to pass the catheter and the other to hold the penis All motions should be gentle and slow not only to avoid discomfort but to facilitate catheterization because rough motions cause the patient to become tense, and the sphincter muscles to contract Unless a stricture is present no difficulty is ordinarily encountered until the posterior urethra is reached where a spastic sphincter or a urethra deformed by a large prostate may cause obstruction Gentle continuous pressure will overcome the spasm of the sphincter more often than strong pressure If the patient is in pain or the urethra oversensitive, analgesics will do much to relieve the spasm of the sphincters There is practically no danger of seriously traumatizing the urethra with a soft rubber catheter Sometimes it is necessary however to use a stilette in the introduction of the catheter and then perforation becomes a real possibility Only hollow tip catheters can be used with a stilette The method of passing a catheter on a stilette is the same as that for passing a sound

Intermittent Catheterization This is sometimes necessary in cases in which the patient is unable to urinate voluntarily as is not infrequent in postoperative patients If such measures are necessary it is better to resort to the catheter before the resistance of the bladder is weakened by over distension A small catheter should be used preferably a size 14 French A convenient schedule of catheterization is four times daily at 7 A M 12 noon 5 P M and 10 P M This scheme does not require interruption of the patient's sleep If there is pus in the urine it is advisable to

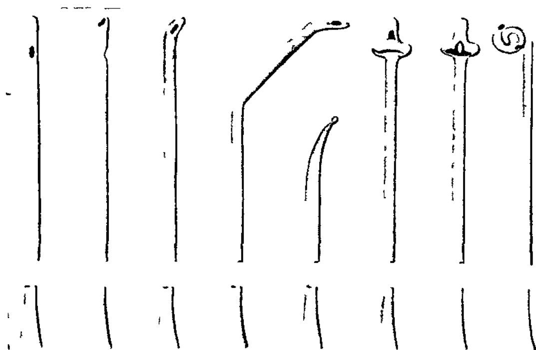


Fig 236 A Soft Rubber Urethral Catheters

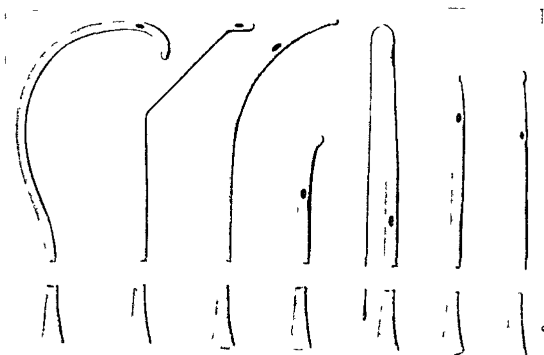


Fig 236 B Woven Catheters

irrigate the bladder once or *twice daily* and instill one ounce of 1 per cent fuchsin The sulfonamides, particularly sulfathiazole and sulfadiazine are of value as a prophylaxis *against urinary infection* *See page 1041 for* details of dosage

Indwelling Catheters These are sometimes necessary when patients cannot void, and are *often used in preparing a patient for prostatectomy* The dangers are epididymitis and urinary infection A size 18 or 20 French catheter is usually suitable The catheter should have at least 2 holes at the end Pass the catheter and when the urine is flowing slowly withdraw the catheter until the stream stops, and then push it in again for a distance of about 1½ inches and fix in this position

The foreskin should be retracted and the glans and corona cleaned as well as the portion of catheter to which the adhesive *is to be fixed* with ether Care should be taken not to spill ether on the scrotum as it burns badly With the prepuce still retracted, three pieces of adhesive about ⅛ inch wide and 5 inches long are run longitudinally along the penis and catheter The three pieces of adhesive are spaced equally about the circumference of the penis Then another piece of adhesive about 4 or 5 inches and 1 inch wide is wrapped around the penis just proximal to the corona, the foreskin re*maining retracted* The corona presents an eminence over which the circular band of adhesive is unlikely to slip The circular band must have a tuck in it to allow for possible expansion of the penis This tuck is made simply by causing the adhesive surfaces of the tape to adhere at one point so that the flap of adhesive so formed protrudes by about ¾ *of an* inch from the ring of adhesive of which it is a part The flap or tuck is made before the circular band of tape is applied Indwelling *catheters should be changed at least weekly* If the urine contains pus the bladder should be irrigated through the catheter with water

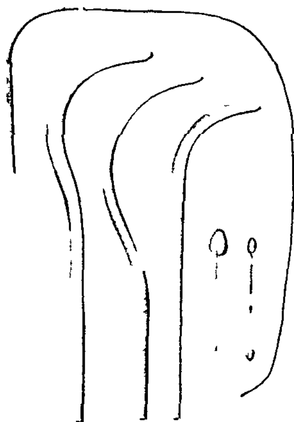


FIG 236 C Sounds and Bougies

saline, or a 2 per cent boric solution at least once a day Blood clots may plug an indwelling catheter and cause severe bladder spasm when the bladder becomes over distended If these clots cannot be washed out with an Asepto syringe a 50 c c syringe should be used in order to bring more suction to bear Keep washing until the return comes back clear If the clots cannot be dislodged the only thing to do is to remove the catheter and insert a new one

Fever is often caused by indwelling catheters Should fever occur it is usually wise to remove the catheter if at all feasible The onset of epididymitis is an indication for removal of the catheter Small bore irrigating tips or other glass tubing should never be used to attach an indwelling catheter to a rubber tube All connections should be as large as the size of the catheter will permit The rubber drainage tube should always be supported by attaching it to the sheet at the side of the bed with a safety pin in order that its weight will not pull on the catheter

Suprapubic Suction Apparatus

The apparatus that is ordinarily used following suprapubic prostatectomy consists simply of an ordinary catheter inside a perforated rubber tube whose lumen is about ½ inch in diameter Suction is obtained by attaching the catheter to a water suction apparatus fixed to a faucet by a plumber This apparatus should be started as soon as possible after the patient returns from the operating room so that there will not be enough time to allow the bladder to fill with clots if there is a tendency to bleed This apparatus usually needs no attention unless the tube slips out of place and has to be replaced or unless it becomes blocked with blood clots in which case it may require removal and cleaning before replacement By no means should one try to plug the space between the catheter and the top of the tube Air must be allowed to come in through this space or the bladder wall may be sucked up against the outside of the tube with such force as to cause necrosis

Foley Alcock Catheter

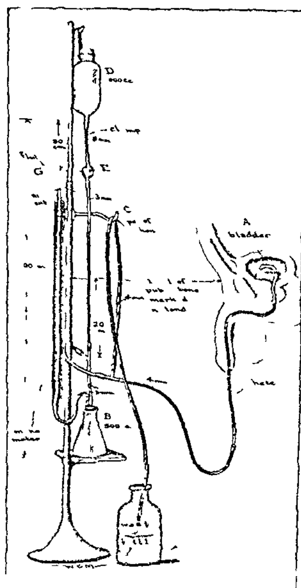
This catheter incorporates three tubes in one One tube is for the water inlet to be used in continuous irrigation the largest tube is for the outflow the small tube with the red tip communicates with a balloon about the circumference of the catheter near its end The balloon is used to keep the catheter in place and also for the purpose of controlling any bleeding which may occur at the bladder neck This control is accomplished by strapping the catheter to the medial aspect of the thigh under tension so that the balloon is forced down against the bleeding points If one limb of the catheter becomes plugged with blood clot reversing the flow may dislodge it Failing this a more forcible attempt should be made to remove the clots through either limb of the catheter with a 50 c c syringe

Decompression of the Bladder

If the bladder contains more than 100 c c of urine it should not be emptied suddenly Various methods are used for gradual decompression the simplest of which is probably releasing the clamp on the indwelling catheter every hour and drawing off 100 c c or more meanwhile forcing fluids by mouth Another simple method that is quite satisfactory is to place a Murphy drip in the rubber tube that leads from the catheter to the bottle and so adjust the rate of the drip by means of a screw clamp that gradual decompression is accomplished Some of the dangers attributed to sudden decompression by some men are discounted by others but there is no question that bladder hemorrhage is a frequent result of sudden emptying of an overdistended bladder

Tidal Drainage of the Bladder

This is an apparatus that continuously lavages the bladder by alternately filling and emptying it The method of Munro is the most efficient yet devised to avoid and treat the bladder complications following spinal injury It alternately fills the bladder to a predetermined degree of intravesical pressure and then empties it by a combination of siphonage and gravity flow the siphon being interrupted when evacuation is complete See figure 237



(From Hermann's Urology W B Saunders Co)

Fig 237 Tidal Drainage Apparatus (after Munro)

Routine Diets

LIQUID DIET

Feedings every two hours of 6 ounces each of any of the following

Meat broths or juices
Albuminized drinks
Milk
Tea
Strained soups
Cereal gruels
Buttermilk
Coffee
Strained or unstrained fruit juices often diluted with water
Cocoa

SOFT DIET

Feedings every three hours of any of the following

Any liquid food,
Cream soups
Buttermilk
Cereals (oatmeal strained)
Blanc mange
Cottage cheese

Stewed fruits without skins and strained if seedy or coarse
Boiled rice
Baked potato
Custards
Milk toast with butter
Ice creams or ices
Milk
Soft cooked eggs
Junkets
Gelatin

LIGHT DIET

Feedings are arranged in meals with intermediate light nourishment The following can be added to the foods in the soft diet
Pureed vegetables
Broiled lamb chops
Tender broiled scraped beefsteak
Bread and crackers
Roast lean leg of lamb
Baked white chicken meat
Jellies or preserves

BLAND DIET

This diet permits no chemical thermal or mechanical irritation

Breakfast

Fruits Stewed or canned prunes peaches pears apricots No pineapple or fruit salad Baked apples without skins applesauce (without cinnamon) Orange juice ½ strength
Cereals Cooked such as farina cream of wheat wheatena oatmeal ralston corn flakes and puffed wheat
Eggs One egg soft boiled or poached
Bread One slice of toasted white bread with butter Marmalade or seedless jelly if desired
Beverages Milk weak postum or Kaffee hag very weak tea or Sanka coffee

Lunch and Supper

Soups Cream soups and plain vegetable soups cooked without meat stock Chicken soup occasionally if skimmed Noodles or alphabet letter or rice
Main Dishes
Chicken steak lamb chop (broiled) chopped meat ball broiled calves liver haddock pike flounder cod halibut striped bass white fish trout baked or broiled never fried or boiled
Baked macaroni and cheese
Soft boiled or poached eggs
Spaghetti without the sauce
Boiled vegetable platter mashed or strained
Vegetables Potatoes baked boiled or mashed Mashed or strained asparagus tips peas carrots squash beets spinach and string beans These may be bought already strained in cans
Salads Small piece tender lettuce chopped fine with dab of mayonnaise
Breads One slice of white bread preferably toasted No rye
Beverages Milk malted milk or very weak tea Sanka coffee once daily
Desserts Simple puddings custard plain jello stewed fruits canned fruits ice cream baked apple applesauce sponge cake and very ripe banana No pineapple
At 10 A M and 3 P M eat any one of the following
Two crackers and a glass of milk
A custard
Cooked cereal with cream
Jello with cream
Tea with buttered toast or zweiback
Vanilla ice cream

REGULAR DIET

This indicates a regular mixed diet furnished to convalescent patients and patients without any dietary restrictions Caloric content from 2000 to 2500 Protein content from 70 to 80 grams daily

CARDIAC DIET (ALSO SEE KARRELL DIET)

This diet is based upon the following principles

1 The food should be simple well cooked and easily digested
2 The total quantity should be small and served in 3 daily portions
3 The heavy meal should be served at noon time
4 The evening meal a relatively light one should be served sufficiently early to insure completion of gastric digestion before retiring

5 Should the caloric content be insufficient when meals are taken as indicated above mid morning and mid afternoon nourishments may be allowed
6 Restrict fluids to 1000 to 1200 c c in 24 hours
7 Should there be a tendency toward constipation the fruit and vegetable content of the diet may be increased, avoiding however those known as gas former

Food Allowed

Beverages Milk, buttermilk milk shakes, malted milk eggnog, tea or coffee allowed once daily
Bread Day old well baked white or brown bread toasted rolls toast zwieback
Cereals Cooked or prepared
Meats Tender rare beef lamb (roast or chops) poultry, fish (baked), oysters
Eggs Any except hard boiled or fried
Vegetables Asparagus string beans, beets, beet greens, carrots celery egg plant lettuce mushrooms okra, potatoes, spinach, squash tomatoes
Fruits Apples apricots blackberries cherries, figs grapes huckleberries oranges peaches pears pineapple plumbs, prunes, raisins raspberries, strawberries
Salads Simple fruit or vegetable with plain mayonnaise, French dressing or boiled dressing
Desserts Cereal puddings custards fruit desserts jello plain ices ice cream sponge cake
Miscellaneous Cream and cottage cheese
Avoid Bulky foods fried foods foods causing fermentation highly seasoned foods pastries elaborate desserts condiments and relishes Avoid overeating and eating at night

INITIAL NEUTRAL DIET FOR SCHEMM TREATMENT OF CARDIAC EDEMA

Six Small Feedings with Protein 60- 0 Calories 2400

Food	Wt gm	Measure
1 Cereal and Cream		
Cereal prepared	15	³ cup
or Cereal cooked	100	¹ cup
or Cereal uncooked	15	1 tbsp
Cream 20%	100	½ cup
Sugar	10	2 tbsp
2 Eggnog		
One egg	—	—
Milk	100	½ cup
Cream 20%	100	½ cup
Sugar and spice	—	—
3 Fruit Bread & Milk		
Prunes	100	½ cup
Bread	30	1 slice
Butter	10	1 pat
Milk	200	1 cup
4 Corn Soup		
Corn puree	70	⅓ cup
Bread	30	1 slice
Butter	10	1 pat
Cream	70	⅓ cup
5 Eggs Toast & Milk		
One egg	—	—
Bread	30	1 slice
Butter	10	1 pat
Milk	200	1 cup
Cream	30	2 tb p
6 Bread and Milk	200	1 cup
Cream 20%	30	1 tbsp
Bread	60	2 slices
Butter	15	2 pats

NOTES

Whole wheat bread prepared without alt butter to be unsalted or washed
Cereal prepared without alt farina cornmeal cracked or ground whole wheat oatmeal puffed rice or puffed wheat only
Any one feeding may be repeated or substituted for another but the two eggs and the milk for the day must be taken Extra bread cereal and eggs may be taken if patient is not overweight
When digestion is weakest prunes should be souffled and the corn soup feeding replaced by feeding 6
When digestion is stronger plums and cranberries may be used in addition to prunes and chicken fresh fish or lamb substituted for the egg in feeding 5
Additional liquids Weak tea or coffee with sugar unsalted weak chicken or beef broth Prune plum cranberry juices well diluted with water (1 4) Water flavored with fruit flavoring
Desserts Clear jello wine jelly angel food or sunshine cakes as desired

Precautions for Home Use

1 *No food or drink other than above* All of each feeding must be eaten
2 *No salt substitutes* except the ammonium chloride furnished you
3 *No soda or alkali medicines* for gas or indigestion other than the calcium carbonate furnished you
4 Measure out three quarts of water and take by 7 00 p m

5 Take two to five drops of the liquid medicine furnished you in a glass of water every hour until 7 00 p m.

FULL NEUTRAL DIET FOR SCHEMM TREATMENT OF CARDIAC EDEMA

Low sodium Acid ash Calories unrestricted

Foods unrestricted as to amount (from which at least two or three servings must be taken for any one meal)

Eggs Two equal one serving (which can be substituted for a meat serving)

Meats Meat, fish or chicken one serving about ¼ lb a day

Bread Plain breads without nuts or raisins Whole wheat bread preferable (five slices or cereal food servings as substitutes in each day)

Cereal These only (one serving a day at least)—oatmeal farina quick cooking cream of wheat cracked or ground whole wheat corn meal mush hominy puffed rice or wheat muffetts

Cereal foods Servings may be taken at any meal and must be taken if meat or egg is not eaten macaroni spaghetti home made noodles corn

Fruit Prunes plums and cranberries For other fruits see below

Foods restricted as to amounts (from which *no more than two* servings should be taken for any one meal)

Vegetables Two servings a day or ½ cup each of any vegetable except parsnips lima beans rhubarb, chard and spinach which are forbidden One small potato equals a serving Use fresh or frozen vegetables or those canned without salt

Fruits One serving of ½ cup of fruit or fruit juice daily except raisins and dates which are forbidden Salads of fruit or vegetable may be made from the above as desired.

Raw fruit and raw vegetable should be used several times a week.

Milk and milk products Two cups of milk daily including that used in preparing food *Cream* Two tbsp in coffee or tea ½ cup for breakfast cereal *Ice cream* Without fruit or nuts one small scoop a day *Cheese* Only unsalted cottage cheese (which may be substituted for a meat or egg serving)

Other foods and food combinations

Soups Many combine vegetables as allowed above with milk allowance or with salt free broths to make soups Salt free clear beef or chicken broth may be taken as desired both with and between meals

Desserts No limit as to amount Plain jello wine jelly plain tapioca angel food or sunshine cake (no cake or cookies made with salt soda or baking powder) *Limited by milk allowance above* Custard junket cornstarch pudding egg nogs ice cream Fruit as indicated above

Beverages One cup of tea or coffee to each meal chocolate made with milk allowance (See Precautions For Neutral Diets)

Neutral foods Which may be taken in any quantity desired Sugar butter oil gelatin salt free salad dressing plain tapioca and plain cornstarch clear sugar candies

Sample Menu of Full Neutral Diet

Breakfast
½ cup orange juice
1 soft boiled egg and/or cereal
½ cup cream
Toast 1–2 slices
Coffee

Lunch
Corn soup
1 poached egg on toast or buttered noodles
Lettuce salad
Bread
Milk 1 cup
½ cup baked custard

Supper
Roast beef
1 small baked potato
½ cup asparagus
Bread
Coffee
½ cup plums

Precautions for Neutral Diets

1 No salt or soda to be used in the cooking or at the table Small amounts of ammonium chloride may be used as a salt substitute Use no other salt substitute such as vegetable salts (Eka etc)

2 Obtain unsalted sweet butter or wash butter free from salt Obtain unsalted bread from baker or make at home Unsalted salad dressing must be made at home

3 *Take no* salted appetizers or salted foods such as salted nuts potato chips sardines olives pickles relishes no cheese except unsalted cottage cheese no smoked or salted meats or fish such as canned salmon or tuna bacon (unless par boiled) ham lunch meats sausage or salt pork.

4 For gas or indigestion *Take no* bicarbonate of soda and no alkali powders or tablets (Tums) *Use* calcium carbonate only Avoid cabbage family turnips rutabagas peppers radishes onions spicy foods and pork

5 *For extra liquids Take none* of the vegetable juices or fruit juices on the restricted list or milk or salted bouillon Use only well diluted plum prune or cranberry juice or water with fruit flavoring or unsalted chicken or beef broth

DRY DIET FOR URINE CONCENTRATION TEST

Breakfast

Dry cereal with sugar syrup or honey
One egg—toast or bread—butter

Luncheon

Roast beef steak or chops
Potatoes boiled or baked
Bread butter or jam

5 Should the caloric content be insufficient when meals are taken as indicated above mid morning and mid afternoon nourishments may be allowed

6 Restrict fluids to 1000 to 1200 c c in 24 hours

7 Should there be a tendency toward constipation the fruit and vegetable content of the diet may be increased, avoiding however, those known as gas formers

Food Allowed

Beverages Milk buttermilk, milk shakes malted milk, eggnog tea or coffee allowed once daily

Bread Day old well baked white or brown bread toasted rolls, toast zwieback

Cereals Cooked or prepared

Meats Tender rare beef, lamb (roast or chops) poultry fish (baked), oysters

Eggs Any except hard boiled or fried

Vegetables Asparagus, string beans beets beet greens carrots, celery egg plant, lettuce mushrooms okra potatoes, spinach, squash, tomatoes

Fruits Apples apricots blackberries cherries, figs grapes huckleberries oranges peaches pears pineapple plumbs, prunes raisins raspberries strawberries

Salads Simple fruit or vegetable with plain mayonnaise, French dressing or boiled dressing

Desserts Cereal puddings custards fruit desserts jello plain ices ice cream sponge cake

Miscellaneous Cream and cottage chee e

Avoid Bulky foods fried foods foods causing fermentation highly seasoned foods pastries elaborate desserts condiments and relishes Avoid overeating and eating at night

INITIAL NEUTRAL DIET FOR SCHEMM TREATMENT OF CARDIAC EDEMA

Six Small Feedings with Protein 60–70 Calories 2400

Food	Wt gm	Measure
1 Cereal and Cream		
Cereal prepared	15	¾ cup
or Cereal cooked	100	½ cup
or Cereal uncooked	15	1 tbsp
Cream 20%	100	½ cup
Sugar	10	2 tbsp
2 Eggnog		
One egg	—	—
Milk	100	½ cup
Cream 20%	100	½ cup
Sugar and spice	—	—
3 Fruit Bread & Milk		
Prunes	100	½ cup
Bread	30	1 slice
Butter	10	1 pat
Milk	200	1 cup
4 Corn Soup		
Corn puree	70	½ cup
Bread	30	1 slice
Butter	10	1 pat
Cream	70	½ cup
5 Eggs Toast & Milk		
One egg	—	—
Bread	30	1 slice
Butter	10	1 pat
Milk	200	1 cup
Cream	30	2 tb p
6 Bread and Milk	200	1 cup
Cream 20%	30	1 tbsp
Bread	60	2 slices
Butter	15	2 pats

NOTES

Whole wheat bread prepared without salt butter to be unsalted or washed

Cereal prepared without alt farina cornmeal, cracked or ground whole wheat oatmeal puffed rice or puffed wheat only

Any one feeding may be repeated or substituted for another but the two eggs and the milk for the day must be taken Extra bread cereal and eggs may be taken if patient is not overweight

When digestion is weakest prunes should be omitted and the corn soup feeding replaced by feeding 6

When digestion is stronger plums and cranberries may be used in addition to prunes and chicken fresh fish or lamb substituted for the egg in feeding 5

Additional liquids Weak tea or coffee with sugar unsalted weak chicken or beef broth Prune plum cranberry juices well diluted with water (1 4) Water flavored with fruit flavoring

Desserts Clear jello wine jelly angel food or sunshine cakes as desired

Precautions for Home Use

1 *No food or drink other than above* All of each feeding must be eaten

2 *No salt substitutes* except the ammonium chloride furnished you

3 *No soda or alkali medicines* for gas or indigestion other than the calcium carbonate furnished you

4 Measure out three quarts of water and take by 7 00 p m

KARRELL DIET REGIME

For 1st Week 200 c c milk at 8 A M , 12 noon 4 P M , and 8 P M No water or salt

On 8th Day Add 1 soft egg and a slice of toast to one of the glasses of milk

On 9th Day An additional egg on toast to one of the milks Later add cereal

On 10th Day Add more egg more toast more cereal later scraped meat and other foods gradually

This diet may be continued only for from 10 to 14 days as it does not contain sufficient water

ACUTE DIARRHEA DIET

After a purge with castor oil avoid all food except Water tea and clear broth When the diarrhea is under control toast cereals crackers and cookies can be added but milk should not be taken

After the diarrhea has been under control for a few days, add boiled milk lean scraped beef white fish, boiled meats hard boiled or soft eggs, later can add puddings and gelatin weakly sugared

CHRONIC DIARRHEA DIET

Same as for later treatment of acute stage avoiding excess fats except some butter Sour orange juice of value Avoid raw milk and cream fruits green vegetables, corn salt meat candy sweets and concentrated sugars

PERNICIOUS ANEMIA

Liver raw or cooked 240 gm or more daily
Red meat $\frac{1}{4}$ lb equals 120 gm
Fruits and vegetables for vitamins
Milk egg potato bread and butter as desired

SECONDARY ANEMIA

Diet Should be rich in iron and copper and high in vitamin content

Moderate high protein is allowed

Food Liver kidney eggs fruits spinach lettuce muscle beef gizzard milk bread and butter as desired

CIRRHOSIS DIET

Breakfast

- *Fruits* Orange juice baked apple apple sauce or stewed fruits as prunes pears peaches with milk and sugar
- *Cereals* Cooked as farina, cream of wheat, wheatena, oatmeal, rolled oats with milk and sugar
- *Eggs* One egg may be taken three times weekly soft boiled or poached on toast with 2 slices of lean crisp bacon
- *Bread* Two slices toasted white bread rolls or corn bread with jam marmalade or jelly Small amount of butter if desired
- *Beverages* Milk half milk and coffee Sanka coffee Postum or weak tea with milk and 2 lumps of sugar

Lunch and Dinner

- *Soups* Small portions of tomato chicken or plain vegetable soup No meat soup or consomme
- *Meats* *Lean* meat or fish twice weekly
  - Meats Roast beef ham or lamb
  - Fish Cod trout weak fish whitefish bluefish flounder striped bass black fish red snapper
  - Chicken—more freely
- *Vegetables* Large servings of potatoes (baked mashed or boiled) or sweet potatoes macaroni or spaghetti Spinach peas beans beet greens beets carrots squash asparagus boiled mushrooms, string beans stewed tomatoes or celery
- *Salads* Lettuce with stewed fruits canned fruits or cooked vegetables with lemon dressing
- *Bread* Two slices toasted white bread rolls or corn bread with jam marmalade or jelly Butter if desired in small amounts
- *Beverages* Milk half milk and coffee Sanka coffee Postum or weak tea with milk and 2 lumps of sugar or malted milk
- *Desserts* Puddings as *bread tapioca corn starch* or sago stewed fruits as peaches, pears plums prunes berries apple sauce, baked apple with milk and sugar Jello junket banana plain cake canned fruit

Intermediate Feedings

A glass of milk malted milk or ovaltine to be taken at 10 A M 4 P M , and at bedtime with zweiback plain or arrowroot crackers breadsticks or toast Jelly or marmalade may be added if desired

Candy Eat sugar-candy or cookies after lunch and dinner

Supper

Two eggs
Bread butter and jam

No liquids are allowed from the evening before the test until the test is finished and no food between meals

RETENTION DIET

This is used in pyloric or esophageal obstruction when minimum residue wanted, and food concentrated, nourishing non irritating and easily assimilated

Give 200 c c every 2 hours from 6 A M to 6 P M if the patient is awake any of the following

Strained cereal diluted with sugar and cream to the consistency of creamed soup
Postum with sugar and cream
Cocoa made with half milk and half cream
Malted milk made with half milk and half cream
Eggnog made with half milk and half cream
Plain ice cream
Plain jello with cream
Junket with cream
Strained cream soup

NO broth or meat extracts and NO plain milk may be used

LOW RESIDUE DIET

Use no condiments such as pepper mustard, horseradish, catsup All meats must be tender and well done Take no very cold drinks

Breakfast

Thoroughly cooked cream of wheat farina or strained oatmeal with butter and cream
Eggs any style except fried if desired
Toast made with stale white bread zwieback butter
Coffee hot water with one third cream or cocoa

10 00 A M

Orange juice tomato juice grapefruit lemonade

Noon

1 Soup clear or thickened with rice or barley flour
2 Dry crisp toast or crackers
3 Tender meat, fowl, or fish, not fried
4 Vegetable puree Tomato jelly
5 Eggs any style except fried
6 Toast made from stale white bread, zwieback, butter
7 Boiled rice thoroughly cooked with cream
8 Custard, stewed fruits, cornstarch puddings gelatins tapioca, plain cake, ice cream
9 Tea or cocoa
10 Strained apple sauce

3 P M

Same as at 10 A M

Evening

Strained cream of vegetable soup
Choice from breakfast

HIGH RESIDUE DIET

Fruits, potatoes bread, lard butter, Swiss cheese soft boiled eggs and milk

FEVER DIET

Albumin water peptonized milk fruit juice glucose, lemonade, simple gruels Gradual return to normal diet

CELIAC DIET

Avoid fats and all carbohydrates with the exception of sucrose in bananas Other foods included are milk cottage cheese boiled skimmed milk egg white, orange or tomato juice lean scraped beef and unsweetened gelatin, unsweetened condensed milk fat free dry milk and lactic acid milk are well tolerated

TUBERCULOSIS DIET

Protein destruction is not as great as in typhoid but protein has its usual specific dynamic action Carbohydrate and protein increase the volume of respiration fat does not

2800–3000 calories daily for sedentary occupation
Plenty of vitamins and minerals Avoid indigestion and obesity
1000 c c milk daily and 4 eggs or more
Protein 120 Gm CHO 230 Gm F 70 Gm per day (3070 calories)
Keep weight just a little above normal

ATONIC CONSTIPATION DIET

Principle Give plenty of foods that will give tone to the muscles of the stomach and intestinal tract so that peristalsis may be increased coarse laxative elements unlimited raw and cooked vegetables and fruits with coarse cereals and other stimulating foods Upon rising take 1–2 glasses of cool water

Breakfast Orange grapefruit or cantaloups baked apples stewed prunes or apricots Shredded wheat biscuit corn and bran flakes rolled oats Eggs soft boiled or poached corn graham or bran muffins toast with butter and honey Cup of hot water and cream (one third cream) or one cup of coffee

10 A M One glass of cool water

Noon

- Vegetable soup All roasts stewed and broiled meats
- Potatoes well mashed baked boiled German and French fried
- Vegetables Onions raw or cooked radishes, olives celery Brussels sprouts sauerkraut cabbage cauliflower lima beans okra fresh stewed or baked tomatoes baked or broiled egg plant carrots spinach asparagus string beans, squash well mashed turnips, stewed celery
- Fruits Stewed or fresh except raw berries
- Salads with mayonnaise or French dressing
- Graham whole wheat rye corn bread or muffins with butter and honey or syrup
- One glass of buttermilk or cool water
- *3 P M* One glass of cool water

Supper Soups stewed or raw fruits and vegetables bread as at lunch All roast stewed or broiled meats potatoes well mashed baked or boiled French or German fried Slices oranges or pineapple nuts molasses candy Canned fruits and vegetables may be used One glass of cool water

Mineral oil 1 tablespoon three times daily No other medicine is to be used at this time Strict cooperation is the keynote of success of the treatment of this condition

The patient should go to stool at a definite time after breakfast and remain for 15 minutes in a completely relaxed state This should be repeated after supper if there has been no bowel movement If still unsuccessful a soap suds enema should be taken later in the evening before retiring

DIET FOR THE CORRECTION OF FLATULENCY AND BORBORYGMUS

Noises produced by gas in the intestinal canal and by its expulsion from the rectum are very annoying and embarrassing but this condition can be alleviated by the patient s adherence to the following foods suggested Generally speaking roughages starches leguminous plants and onions should be eliminated from the diet entirely

Foods Not Likely to Cause Gas

- Vegetables especially green artichokes asparagus spinach string beans green peas cooked celery summer squash and French carrots
- Limited quantity of boiled baked or mashed potatoes
- Rice barley, farina cornstarch arrowroot oatmeal cream of wheat and other ordinary cooked breakfast foods
- Water tea milk and buttermilk
- Fresh meat or white fish game poultry once a day
- Eggs in moderation
- Cottage cheese
- Limited amount of butter
- Toast bread and zwieback
- Plain cake and puddings
- Fresh fruit—apples grapes pears figs peaches oranges grapefruit pineapple juice
- Salads of lettuce and other fresh green vegetables raw or cooked

Foods to Avoid

- Meats Canned salted preserved or spiced
- Fish Herring sardines in oil mackerel salmon shellfish
- Stews goose domestic duck oysters
- Old cheese cream cheeses except cottage cheese
- Dry beans corn sprouts cole slaw, cabbage cauliflower sauerkraut raw vegetables garlic and onion
- Rich soups, berries figs preserves gravies nuts sweets pastry fats oils and alcoholics

Note to Patient The fluid intake should be reduced to 2 quarts daily Dry heat or hot

Avoid Meat extracts, meat fats, grease gravies All foods fried, hashed or warmed over Inner organs such as, brain, liver, kidneys, sweet breads, or rich foods and highly seasoned foods Oils, as olive oil, cod liver oil, salad dressings Heavy cheeses nuts, olives spiced foods Acid foods, condiments alcohol Rough foods as cabbage, cucumbers pickles, bran and wholewheat products

Note With digestive disturbances, salads raw fruits, and raw vegetables should be omitted all vegetables *should be mashed or strained*

GALL BLADDER DIET

Cholecystitis and cholelithiasis require a low fat and low fiber diet and free from highly seasoned foods and pastries If the patient is obese, the caloric content should be reduced Note Not *only* eggs but egg preparations should be omitted from the diet as well as cream, cream sauces and ice-cream, fish must be baked or broiled, *not* sauted Salmon, herring, mackerel and pompano should be avoided

Hygiene This should include rest periods throughout the day the avoidance of cross ventilation or extremes of temperature

Breakfast Ripe fruits, skimmed milk or plain milk Bananas are too heavy Cooked cereals are preferable but if there is no gastro duodenitis prepared cereals may be given Sanka Coffee, Kaffee Hag or milk

Luncheon Consomme and puree soups (without cream) Vegetables prepared by rapid boiling and NOT in deep fat Cabbage Brussel sprouts and cauliflower may be given in small amounts and without cream sauces but NO parsnips radishes or turnips nor French dressing or mayonnaise When lemon juice is not satisfactory a good French dressing can be made with lemon juice and mineral oil flavored with salt and pepper and a dash of mustard

Desserts Ices junkets gelatin preparations stewed or very ripe fruits

Dinner Requires the most careful attention NO fatty meats pork fish (salmon shad, herring, sardines) are allowed

Lamb lean beef, hamburg steak roast beef and all poultry except guinea hen, can be taken and sea bass and filet of sole baked *or broiled*

HIGH VITAMIN ACID ASH DIET (IN RENAL STONES AND INFECTIONS)

Soups Broths and cream soups of meats or suitable vegetables

Meats All meats, poultry, fish, cheese—twice daily

Eggs 1 or 2 daily

Fruits Prunes, cranberries plums as desired Watermelon, grapes, fresh pears apples and orange juice—not more than 2 servings daily

Vegetables Corn (fresh and canned) as desired

Asparagus, green peas onions, pumpkin, squash turnips and radishes—1 or 2 servings daily

If only 1 of the above group of vegetables is chosen one of the following may be taken Mushrooms cauliflower string beans, tomatoes, cabbage and tomato juice

Salads Of the fruits and vegetables allowed

Bread Soda crackers whole wheat bread white bread—at least 3 slices daily, and more as desired

Cereals Wheat germ oatmeal cornmeal, shredded wheat, macaroni rice noodles, spaghetti,—at least 2 servings daily

Milk 1 pint

Cream ½ pint

Nuts Walnuts, peanuts as desired

Yeast 2 cakes daily

Cod Liver Oil 2 teaspoons daily

Miscellaneous Butter, sugar cornstarch tapioca tea coffee—as desired

Foods to Be Omitted Vegetables and fruits of all kinds except those listed

Evaporated or condensed milk

Dried or fresh chestnuts coconuts, almonds

Olives olive oil and molasses

NOTE The urine should be tested with litmus morning and evening for acid If urine is not acid from diet alone ammonium chloride or sodium phosphate should be added

Take a teaspoon of cod liver oil morning and evening

High Carbohydrate Diet

Regular diet omitting meat and eggs extra portions of vegetables and fruits rice macaroni puddings etc, may be given

High Carbohydrate Low Fat

This indicates House Diet with extra high carbohydrates added and fatty foods such as butter milk cream mayonnaise eggs bacon etc eliminated This is approximately carbohydrate 300 gm, protein 70 gm fat 20 gm Total 1600 calories

High Fat Diet

Regular diet plus butter fat meats oils creams etc

Edentulous Diet

This indicates a House Diet so modified in texture and consistency that it needs little mastication

Meulengracht Diet

7 30 A M Tea white bread butter 10 00 A M Oatmeal with milk white bread and butter 12 30 P M Meat balls broiled chop omelet fish balls vegetable gratin or fish gratin mashed potato vegetable puree and soups stewed apricots applesauce gruel or rice tapioca pudding 3 00 P M Cocoa 6 00 P M White bread and butter sliced meats cheese and tea

The results obtained are probably due to the rapid replacement of plasma proteins

REDUCTION DIET FOUR HUNDRED AND FIFTY CALORIES (1[illegible])

Protein [illegible] gm Fat 9 gm and Carbohydrate 32 gm

Menu Plan

Breakfast	
6 per cent fruit	100 gm
Skimmed milk	[illegible] gm
Coffee	ad libitum
Lunch	
Meat or fish	60 gm cooked
3 per cent vegetable	100 gm
Skimmed milk	100 gm
Dinner	
Meat or fish	90 gm cooked
3 per cent vegetable	100 gm
Skimmed milk	100 gm

Sample Menu

Breakfast	
Melon	100 gm.
Skimmed milk	200 gm
Coffee	ad libitum
Luncheon	
Boiled shrimp	100 gm.
Lettuce and tomato salad	100 gm
Skimmed milk	100 gm
Coffee	ad libitum
Dinner	
Lean corned beef	90 gm cooked
String beans	60 gm, cooked
Cole slaw (raw cabbage with vinegar and seasonings)	40 gm
Skimmed milk	130 gm
Coffee	ad libitum

Note that 100 gm of shellfish has the same caloric value as 60 gm of lean meat or fish

REDUCTION DIET SIX HUNDRED CALORIES (17)

Protein [illegible] gm Fat 9 gm and Carbohydrate 65 gm

Menu Plan

Breakfast	
6 per cent fruit	100 gm
Bread	30 gm
Skimmed milk	100 gm
Coffee	ad libitum
Lunch	
Meat or fish	60 gm cooked
3 per cent vegetable	100 gm
6 per cent fruit or vegetable	100 gm
Skimmed milk	200 gm
Tea or coffee	ad libitum
Dinner	
Meat or fish	90 gm cooked
3 per cent vegetables	
1 raw	100 gm
1 cooked	100 gm
9 per cent fruit or vegetable	100 gm
Milk	100 gm
Tea or coffee	ad libitum

Sample Menu

Breakfast	
Melon slices	100 gm
Bread toasted dry	30 gm
Skimmed milk	100 gm
Coffee	ad libitum
Luncheon	
Cottage cheese with chives	90 gm
Head lettuce (dressed with tarragon vinegar and condiments)	100 gm
Raspberries	[illegible]0 gm
Skimmed milk	200 gm.
Dinner	
Ground beef patty broiled	100 gm
Beet greens with lemon	100 gm cooked
Sliced tomato	100 gm
Peaches water packed	100 gm
Skimmed milk	100 gm
Coffee	ad libitum

compresses applied to the abdomen usually will only require a short time in most cases until relieved. A soapsuds enema will often relieve an attack. Mild laxatives such as mineral oil or petrolagar frequently control the tendency to excessive gas formation.

DIETS FOR DIABETICS

See section on "Management of Diabetes," pages 579-591

FORMULA FOR JEJUNAL FEEDINGS

No 1

Gelatin, 30 grams
Lactose, 90 grams
Water, 32 Oz
Juice of one orange

No 2

Cereal, gruel 16 Oz (oatmeal, barley or cornmeal)
Milk 14 Oz
Cream 4 Oz
Lactose 3 Oz

No 3

Cereal gruel 12 Oz (oatmeal, barley or cornmeal)
Milk, 32 Oz
Cream 4 Oz
Lactose, 4 Oz

Dr Gwathmey recommends two ounces of any of the above feedings through the duodenal or jejunal tube every hour if tolerated.

POST OPERATIVE DIETS

Liquid Diet without Milk or Fat

Breakfast

Orange juice or carbonated drink
Coffee or tea

Mid Morning

Cereal gruel
Sugar if desired

Noon Meal

Consomme
Coffee or tea Postum
Sugar
Ices without fiber or other solids

Mid Afternoon

Jello (Plain)

Supper

Fat free broth
Cereal gruel
Ginger ale or carbonated drink

8 P M

Hot lemonade
Hot cocoa without milk (provided patient is not hypersensitive to chocolate)

*Liquid Diet with Milk**

Breakfast

Orange juice or tomato juice
Cereal gruel
Coffee with cream and sugar or hot chocolate

Mid Morning Ice cream

Noon Meal

Strained broth without fat

Mid Afternoon

Eggnog

Supper

Consomme or strained oyster stew
Plain jello

Bedtime

Hot chocolate

High Caloric Diet

Regular or light diet plus extra milk, cream, eggs, custards, milk drinks. It indicates a *House Diet* in the hospital plus supplementary foods to yield 3500 calories or more.

High Protein Diet

Regular diet plus extra meat, eggs, cheese, custards.

Low Protein Diet

Regular diet omitting meat and all but one egg daily plus extra portions of vegetables and fruits.

* Many people are hypersensitive to milk, others to chocolate. Hypersensitivity to these two foods should be ruled out before they are included in the menu.

High Carbohydrate Diet

Regular diet omitting meat and eggs, extra portions of vegetables and fruits rice macaroni puddings etc may be given

High Carbohydrate Low Fat

This indicates "House Diet with extra high carbohydrates added and fatty foods such as butter milk, cream mayonnaise eggs bacon etc, eliminated This is approximately carbohydrate 300 gm, protein 70 gm fat 20 gm Total 1600 calories

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The results obtained are probably due to the rapid replacement of plasma proteins

REDUCTION DIET FOUR HUNDRED AND FIFTY CALORIES (17)

P ot n 60 gm Fat 9 gm d C bohyd at 32 gm

M u Pl

B kfa t	
6 pe nt fru t	100 gm
Skimm d m lk	200 gm
Coff	ad l l tum
L n h	
M at fi h	60 gm ook d
3 pe ce t eg table	100 gm
Sk mmed m lk	100 gm
D	
M at fi h	90 gm cook d
3 per ce t v g tabl	100 gm
Sk mmed m lk	100 gm

Sample M nu

B akf t	
Mel n	100 gm
Sk mmed milk	200 gm
C ffe	ad l b tum
Lun he n	
Boil d shrimp	100 gm
Lettuce and tom to salad	100 gm
Skimm d m lk	100 gm
Coffe	ad l b tum
D ner	
Lean co n d beef	90 gm cook d
St ng beans	60 gm ooked
C l slaw (aw cabbag th vinega and seas gs)	40 gm
Sk mm d m lk	100 gm
Coff	ad l b tum

Note that 100 gm of shellfish h the cal r c alue of 60 gm of l an m at or fish

REDUCTION DIET SIX HUNDRED CALORIES (17)

Prot n 65 gm F t 9 gm and Ca bohyd at 65 gm

M u Pl n

B kf t	
6 pe cent fru t	100 gm
B ead	30 gm
Skimmed m lk	100 gm
C ffe	l l b tum
L h o	
M at fish	60 gm oo ed
3 per e t g t bl	100 gm
6 pe t fru t or getabl	100 gm
Sk mmed m lk	200 gm
Te coffee	ad l b tum
D	
M t or fish	90 gm cooked
3 p nt egetables	
l aw	100 gm
l oked	100 gm
9 p r nt f uit or g table	100 gm
M lk	100 gm
T a or coff	d l b t m

S mpl M

B akf t	
M l l	100 gm
B e d t ast d d y	30 gm
Skimmed m lk	100 gm
C ff	d l b tum
L h	
C ttage che se th l es	90 gm
H d l ttuc (d sed w th t on e ga d nd m nts)	100 gm
R spbe	0 gm
Skimmed m lk	00 gm
D n	
G ound beef patty b o led	100 gm
B t gre ns w th l m n	100 gm oo ed
Sl ed t mato	100 gm
Pe h w t p cked	100 gm
Sk mm d m lk	100 gm
Coff	ad l b tum

REDUCTION DIET EIGHT HUNDRED CALORIES (17)

Protein 73 gm Fat 28 gm and Carbohydrate 65 gm

Menu Plan

	Household measure	Weight gm
Breakfast		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Lunch		
Meat or fish	2 oz	60
3 per cent vegetable	1 serving	100
6 per cent vegetable or fruit	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5
Dinner		
Meat or fish	3 oz	90
3 per cent vegetable (1 raw 1 cooked)	2 servings	200
9 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5

Sample Menu

	Household measure	Weight gm
Breakfast		
Strawberries	½ cup	60
Poached egg	1	50
Whole wheat toast	1 slice	30
Butter	1 teaspoon	5
Black coffee	ad libitum	ad libitum
Luncheon		
Crab meat salad		
Diced celery	½ cup	60
Crab meat	½ cup	120
Minced onion and lemon		
Lettuce leaves		
Mayonnaise	1 tablespoon	15
Melon	1	60
Skimmed milk	1 glass	200
Dinner		
Beef steak broiled	3 oz	90
Asparagus with butter	6 stalks	100
	6 teaspoons	10
Lettuce salad		
Lettuce	½ head	50
Tomato	1 small	100
Dressing	ad libitum	ad libitum
Pear	½ cup	120
Skimmed milk	1 glass	200

Ingredients 1 egg 1 teaspoon salt 1 teaspoon mustard 2 cups liquid petrolatum 2 tablespoons vinegar and ½ teaspoon paprika

REDUCTION DIET ONE THOUSAND CALORIES (17)

Protein 75 gm Fat 42 gm and Carbohydrate 85 gm

Menu Plan

	Household measure	Weight gm
Breakfast		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Coffee ad libitum with milk	1 oz	30
Luncheon		
Lean meat fish or	2 oz	60
Cottage cheese	3 oz	90
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Bread	1 slice	30
Butter	1 teaspoon	5
Whole milk	1 glass	200
Dinner		
Lean meat or fish	3 oz	90
3 per cent vegetable (1 raw 1 cooked)	2 servings	200
9 per cent fruit	1 serving	100
Whole milk	1 glass	200
Tea or coffee	ad libitum	ad libitum

Sample Menu

	Household measure	Weight gm
Breakfast		
Strawberries	½ cup	100
Boiled egg	1	50
Whole wheat toast	1 slice	30
Butter	1 teaspoon	5
Coffee with milk	1 oz	30
Lunch		
Cottage cheese	3 tablespoons	65
Kale	½ cup	100
Cabbage and celery salad	½ cup	100
Mineral oil dressing	1 tablespoon	15
Whole wheat bread	1 slice	30
Butter	1 teaspoon	5
Whole milk	1 glass	200
Dinner		
Roast beef (fat trimmed)	3 oz	90
Broccoli	½ cup	100
Cucumber and radishes	½ cup	50
Pear	1	12
Whole milk	1 glass	200
Black coffee	ad libitum	ad libitum

FRUITS AND VEGETABLES CLASSIFIED ACCORDING TO THEIR AVERAGE CALORIC VALUES PER HUNDRED GRAMS*

16 calories — 3 per cents Carbohydrate 3 gm — Protein 1 gm

Vegetables
- Asparagus
- Bamboo shoots
- Beans green†
- Beans wax†
- Bean sprouts
- Broccoli
- Cabbage
- Cabbage Chinese
- Cauliflower
- Celery
- Chard
- Chicory
- Cress water
- Cucumbers
- Endive
- Escarole
- French endive
- Lettuce
- Mustard greens
- Radishes
- Sauerkraut
- Sorrel
- Spinach
- Squash summer
- Tomatoes
- Tomato juice
- Turnip tops

Fruit
- Rhubarb

28 calories — 6 per cents Carbohydrate 6 gm — Protein 1 gm

Vegetables
- Carrots canned
- Collards
- Dandelion greens
- Eggplant
- Kale
- Kohlrabi
- Leeks
- Lambs quarters
- Okra
- Parsley
- Peppers
- Pumpkin
- Squash winter
- Turnips

Fruit
- Blackberries
- Melons
- Strawberries

40 calories — 9 per cent Carbohydrate 9 gm — Protein 1 gm

Vegetables
- Brussels sprouts
- Beets
- Carrots fresh
- Onions fresh
- Peas canned†
- Rutabagas

Fruit
- Applesauce canned unsweetened
- Apricots water packed
- Blueberries
- Cranberries
- Gooseberries
- Grapefruit
- Grapefruit juice
- Peaches
- Pears
- Loganberries
- Lime
- Lemons
- Raspberries
- Tangerines

52 calories — 12 per cents Carbohydrate 12 gm — Protein 1 gm

Vegetables
- Lima beans green canned†

Fruit
- Apricots fresh
- Cherries sour fresh
- Oranges
- Orange juice
- Pineapple
- Plums
- Kumquats

64 calories — 15 per cents Carbohydrate 15 gm — Protein 1 gm

Vegetables
- Parsnips
- Kidney beans red canned†
- Peas fresh†

Fruits
- Huckleberries
- Grapes
- Mangos
- Nectarines

96 calories — 18 per cents Carbohydrate 18 gm — Protein 4 gm

Vegetables
- Corn canned sweet
- Potatoes

Fruit
- Prune juice
- Figs fresh
- Grape juice
- Pomegranates

* Adapted from Chatfield C and Adams G Proximate Composition of American Food Materials Circular 549 U S Dept of Agriculture June 1940

† The protein content of this food is greater than 1 gm per cent. They should be omitted when weighed diets are prescribed or the additional calories taken into account

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